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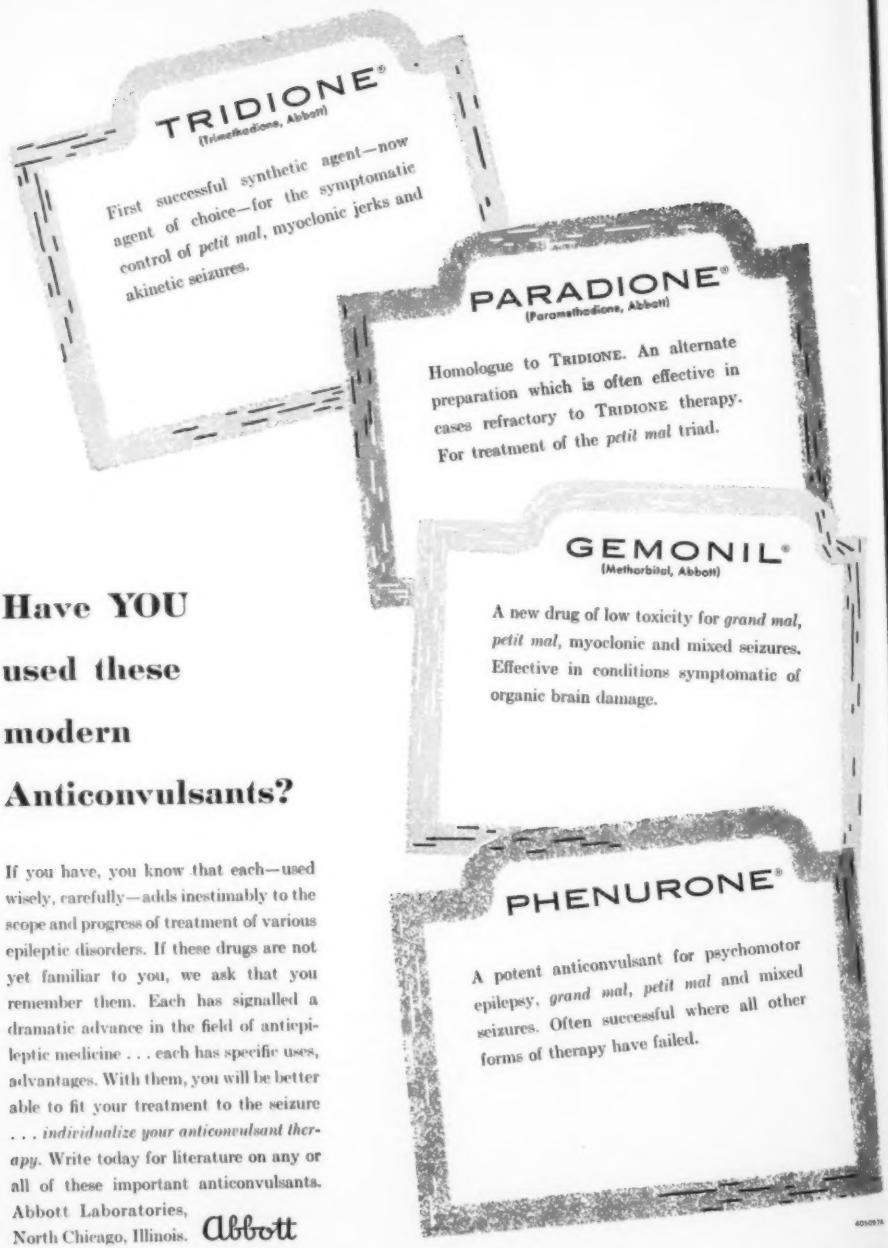
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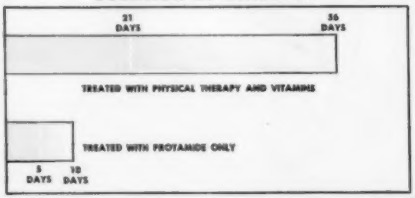

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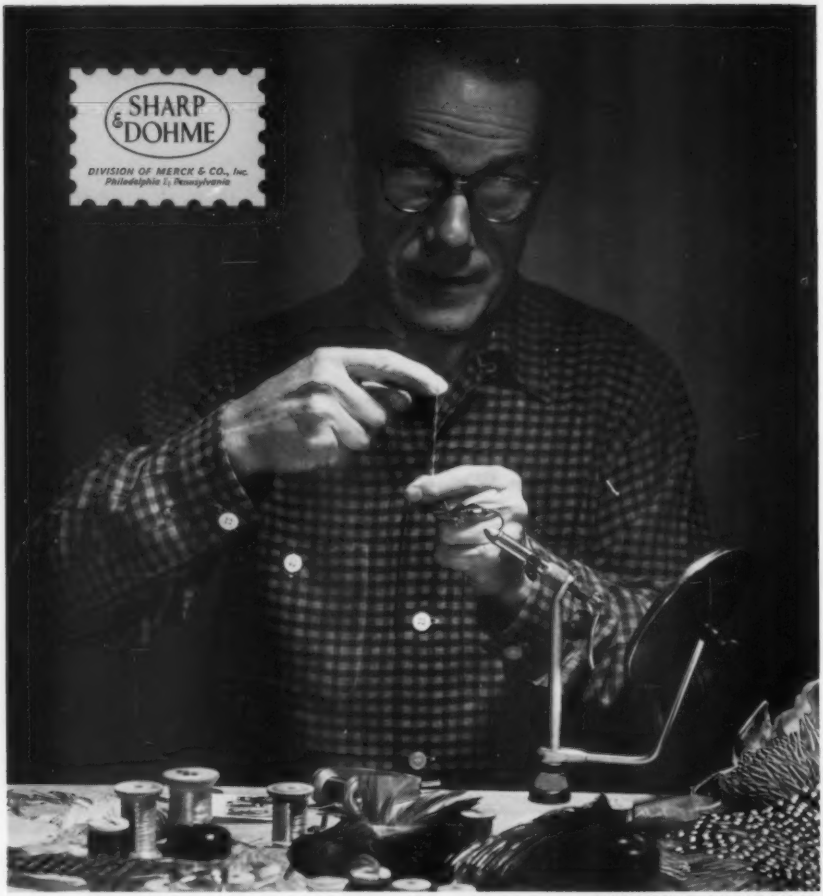

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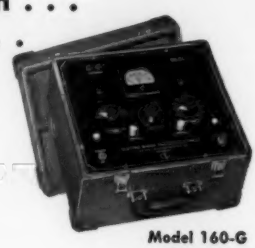

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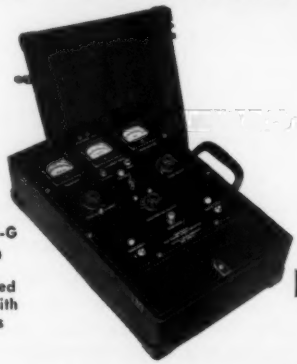

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2. Whitty, C. W. M.: Brit. M. J. 2:540 (Sept. 5) 1953.

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Neurology

Metrazol Activation as a Diagnostic Adjunct in Electroencephalography

A Reevaluation

Floy Jack Moore, M.D., Peter Kellaway, Ph.D. and Nina Kagawa

In spite of considerable information obtained by the use of routine electroencephalography in the diagnostic evaluation of epileptic disorders, there continues to be an important percentage of patients in whom routine electroencephalography does not provide definitive or definite diagnostic information. It is generally accepted that approximately 10 to 25 per cent of epileptics have "normal" routine interseizure electroencephalograms.[1–3] Even among the 75 to 90 per cent with abnormal records, a considerable number of the abnormalities are nonspecific in character and may be found in a significant portion of controls. For example, Gibbs, Gibbs, and Lennox[2] found 83 per cent abnormalities in 730 adult epileptics, while similar abnormalities occurred in 15.8 per cent of 1000 normal controls.

As Merlis[4] has pointed out, "the occurrence of paroxysmal or seizure discharges" while not pathognomonic is considered the most reliable diagnostic interseizure characteristic. In the Gibbs study mentioned above such dis-

From the laboratory of clinical electrophysiology, department of physiology, Baylor University College of Medicine, and the Veterans Administration Hospital, Houston, Texas.

This investigation was supported by the Medical Research Development Board, Office of the Surgeon General, Department of the Army under Contract No. DA-49-007-MB-485.

Read, in part at the meeting of the American League Against Epilepsy, Cambridge, Massachusetts, August 22, 1953.

charges occurred in 29.3 per cent of their epileptic series as opposed to 0.9 per cent of their controls. In later studies they found "seizure discharges" in 38 per cent of the routine waking records of out-patient epileptics.[5]

Thus it is clear that a specific activation technic is necessary in order to increase the diagnostic efficiency of electroencephalography. Various procedures for this purpose have been employed. These include hydration,[6,7] alcohol,[6] insulin,[8,9] Tridione[6] (for grand mal patients, because of the observation that it often made this group "worse"), pneumoencephalography,[10] electric shock,[6] penicillin,[6] various antihistamines,[11] sodium cyanide,[6] photic driving,[12,13] acetylcholine,[6] scopolamine alpha chloralose combination,[14] sleep,[5,7,15,16] hyperventilation,[7,17] and Metrazol. It can be said that, with the exception of sleep, hyperventilation, and Metrazol, none of these has proved consistently useful. Photo-Metrazol has been reported to be helpful,[12,13] but these results are dependent upon the unproved assumption that Metrazol by itself is specific. Photic activation alone has been useful according to some observers, but far more work needs to be done here concerning the parameters of normality.

Metrazol has recently received considerable support as an effective activation agent, and when given according to certain specific procedures, it is accepted by many workers as a valid diagnostic test.

REVIEW OF THE LITERATURE

Results of the many investigations of Metrazol activation have been substantially in agreement as to the fact that it may be used to bring out latent electroencephalographic abnormalities in patients with convulsive disorders, and that comparable technics do not produce such abnormalities in a significant number of controls. Kaufman and co-workers[6] reported focal activation in 60 per cent of 97 posttraumatic epileptics given 200 mg. rapidly intravenously; no controls were mentioned. Cure and his group[18] using a rapid method (total dose of 2.6 mg./kg. initially) reported 49 per cent activation out of 55 epileptics and no activation in six controls. With a slow technic (20 mg. every 30 seconds up to a total dose of 400 mg.) they found 80 per cent activation in 50 epileptics and 15 per cent activation in 31 nonepileptic controls. Renault[19] did not quote figures but stated that Metrazol is "of incontestible value" during diagnostic examination of epileptic patients. Merlis and co-workers,[4] using a technic of 25 mg. every 30 seconds up to 500 mg., reported 47 per cent activation in 57 epileptics and no activation in 38 controls. Later in a larger series of epileptics they reported 62 per cent activation.[16] Matthijs[20] stated that 80 per cent of epileptics show "changes;" no controls were mentioned. Peniche[21] obtained a marked increase in the percentage of abnormal tracings in individuals "in whom the existence of epilepsy was sufficiently verified." In 100 control subjects (psychiatric patients) he stated that 6 per cent had abnormal tracings with Metrazol. His method consisted, in part, of giving 200 mg. of a 10 per cent solution intravenously during 1 minute. Hutchinson,[22] using a technic of 0.022 cc. of a 10 per cent Metrazol solution

per kg. body weight initially, followed by 0.011 cc./kg. body weight at 30 second intervals up to approximately 400 mg., found 83 per cent activation in 36 epileptics; in 64 individuals with clinical histories suggestive of epilepsy he obtained activation in 20.3 per cent; no controls are mentioned. Cohn and his co-workers,[8] giving 100 mg. per minute up to 300 mg., reported activation in 14 of 26 epileptics; in 15 controls ("narcoleptic and aggressive behavior") seven showed activation; in 118 unselected "controls" from the neuropsychiatric wards 17 out of 118 showed activation. Fuglsang-Frederiksen,[23] using a fast technic of 2 mg./kg. of body weight initially followed by 1 mg./kg. at 30 second intervals up to 350 mg., stated that 82 per cent of 96 epileptics showed activation; one out of 63 "control" subjects activated; and of 92 individuals with syncope, 55 per cent activated. It is to be noted that different technics were utilized by the various investigators and seemed to affect the percentage of activations produced. More will be said about this later.

The criteria of abnormality is not always explicitly stated by the various authors, but many appear to agree with Merlis that activation is defined as the elicitation of electrographic seizure discharges – that is, "a paroxysmal occurrence of high voltage activity, faster or slower than the background rhythms, or the appearance of spikes, sharp waves, or mixtures of these with irregular slow wave activity appearing either paroxysmally or in a more or less continuing fashion."

Nearly all the investigators who employed Metrazol found some degree of activation in their controls, but apparently considered this percentage to be insignificant. Several studies of nonepileptic psychiatric patients, with technics not always comparable to those used by other groups, reported relatively high percentages of so-called positive responses. Cohn and co-workers[8] used neuropsychiatric patients for controls and, employing a technic of 100 mg. of Metrazol intravenously per minute up to 300 mg. total dose, produced spike and wave discharges in seven out of 15 cases in one series and 17 out of 118 in another series. Smith and co-workers,[24] in a study of 48 nonepileptic neuropsychiatric patients, using a rapid intravenous dose with increasing dosages at subsequent tests, found "electroencephalographic changes" in all patients, and 3 per second spike and wave pattern in 33 per cent. Browne-Mayers and Straub[25] used the technic of 20 mg. every 30 seconds up to a total dose of 400 mg. in 61 nonepileptic psychiatric patients and found 12 "epileptiform wave patterns," with all positive responses occurring in those with moderately abnormal or "epileptoid" features in their pre-Metrazol electroencephalograms.

Recently Buchtal and Lennox[26] reported upon 682 normal subjects (air force applicants) studied electrographically at rest and during provocation with hyperventilation, photic stimulation, and Metrazol. They reported the incidence of Metrazol-induced paroxysms to vary from 15 per cent among subjects with normal to 50 per cent in subjects with a paroxysmal electroencephalogram. Yet they concluded that "this study confirms the diagnostic value of Metrazol provocation." They used the technic reported by Fuglsang-

Frederiksen in which 2 mg. of Metrazol per kg. of body weight was given intravenously initially, followed by 1 mg. per kg. of body weight in each subsequent 30 seconds up to a total dose of 300 mg.

We believe that activation in nonepileptic patients, reported by nearly all workers, makes necessary a reevaluation of the whole problem of Metrazol activation.

SELECTION OF PATIENTS

A reevaluation of the usefulness of Metrazol-activated electroencephalography as a diagnostic adjunct was carried out in a series of 250 selected patients between the ages of 17 and 65. One hundred and twenty of these were subjects meeting strict criteria of normality – that is, asymptomatic individuals who had never had convulsions, fainting spells, central nervous system disease, or any symptoms which might be construed as such, and who, in addition, had had a negative family history (only a very small number, 11, of this group had a psychiatric diagnosis). A second group of 49 patients with proved convulsive disorders were studied. Because activated electroencephalography is most often employed to evaluate existence of convulsive disorders in patients presenting indefinite or equivocal ictal symptoms, an additional group of 81 patients with such symptoms as dizzy spells, syncope, amnesic episodes, headaches, and so on, were investigated. These are referred to as the equivocal group.

METHOD

In preliminary studies various technics were tested and discarded for many reasons which will be discussed later. It was concluded that the slow technic is the best all-around method. A 5 per cent solution of Metrazol, that is 50 mg. of Metrazol per cc., is injected at the rate of 0.5 cc. (25 mg.) every 30 seconds. This is given rapidly intravenously during the first to third second of each injection period. A total of 500 mg. is given unless activation intervenes. Initially a routine electroencephalogram, which included a sleep study in the abnormal group, was made. At the first indication of paroxysmal changes or build-up, or the appearance of focal changes, the injection was temporarily or completely discontinued. Intravenous Nembutal has been used if such activity increases. In addition, sensory stimulation, such as slapping the patient on the chest or talking to him, was helpful in breaking up augmenting epileptic discharges. No attempt was made to change the dosage or rate of injection in relation to the weight of the individual as has been suggested by Jasper[27] and others.

The procedure was not unpleasant for the majority of individuals tested. Side effects were minimal and disappeared within five minutes after finishing the Metrazol injection. With this technic, subjective complaints and movement did not interfere to any appreciable extent with the performance of the test or obscure the record with artifact, especially when reassurance and a careful explanation of the mechanics of the test and amount of dizziness ex-

pected was provided. Only four patients of the 250 in the entire series had a convulsion during or soon after the Metrazol test. There were no seizures in the normals, one in the equivocal group, and three in the convulsive group. One of the patients in the convulsive group had a four minute build-up electrographically prior to his clinical seizure, which could have been prevented. The other three patients developed abnormal electroencephalograms which culminated in convulsions within 15 to 20 seconds; these were considered as not being preventable. Two of these had had recent and frequent seizures and probably should not have had the test performed at that time.

Two patients in the convulsive group had negative Metrazol reactions while on medication, but were definitely positive when taken off their medication for from three to five days. Except for this factor no attempt was made to increase positive results by repeated testing. Several patients on whom the test was repeated were also positive and showed the same type of activation as on the initial test.

The generally accepted criteria of positive Metrazol activation are the production of spike and wave patterns, paroxysmal high voltage slow waves, spikes, or the elicitation of clearly discernible and consistent focal abnormalities. We have attempted to test the validity of these criteria.

RESULTS

Table 1 shows the breakdown of the entire group in terms of positive and negative activation.

The epileptic group gave a quite high percentage of positive activation (77.5 per cent). In analyzing the negative activations in the convulsive group, it is interesting to note that six of the 11 negative Metrazol activations were alcoholics who had seizures only with alcohol or soon after overindulgence. One of these had had repeatedly negative electroencephalograms except for one record which was taken after he had been intoxicated. This record demonstrated a paroxysmal dysrhythmia. If these six are eliminated from the convulsive group, then the percentage of positive activations rises to 88 per cent.

With the exception of a few cases of poorly defined or inconsistent focal abnormalities in the temporal regions all pre-Metrazol focal activity was ac-

TABLE 1
SUMMARY OF POSITIVE AND NEGATIVE RESULTS OF METRAZOL ACTIVATION

Group	*Total*	*Positive activation*	*Negative activation*	*Normal pre-Metrazol EEG*	*Abnormal pre-Metrazol EEG*
Normal controls	120	42 (35%)	78 (65%)	105	15
Equivocals	81	38 (47%)	43 (53%)	48	33
Definite convulsives	49	38 (77.5%)	11 (22.5%)	41	8
Total	250	118 (47.2%)	132 (52.8%)	194	56

centuated or more clearly delineated (12 cases). In 14 cases focal abnormalities were demonstrated with Metrazol that were not found in one or more routine studies. When focal abnormalities were found with Metrazol activation, these individuals invariably had a clinical history or epileptic manifestations functionally and anatomically consistent with the electroencephalographic localization. Not all of these were patients with focal epilepsy – some had vascular lesions or localized cerebral trauma without convulsions. While it seems true that all epileptogenic tissue is abnormally responsive to Metrazol (perhaps this can only be demonstrated with electrocorticography), it is not true that all tissue abnormally responsive to Metrazol is epileptogenic.

Positive tests were obtained in 47 per cent of the equivocal group. These data concerning this group and the convulsives are essentially in agreement with the results of other investigators.

However, 35 per cent of the normals had definitely positive tests. This group was examined carefully and an important fact emerged, namely that age seemed to be a significant factor in terms of Metrazol reactivity. When a distribution curve was made relating Metrazol response to age, there appeared to be a definite trend with a marked tendency for the numbers of positive responses to fall off after the age of 30. Figure 1 shows this in graph form. Table 2 shows these same results numerically. Positive activations occurred in 54.2 per cent of 59 individuals under the age of 30 meeting strict criteria of normality. Of 61 individuals over the age of 30 in the same group, only 16.4 per cent had a positive activation. It will be noted from the breakdown that while age is an important factor in response to Metrazol in the normal group, it seems to have little or no significance in the convulsive group.

A further division of our series into ten year age groups was not statistically significant because of the small numbers in each group, but suggested that activation was maximal in the younger individuals and declined progressively with increasing age. This was most striking in the control group.

Of these positive activations in the normal group under the age of 30, 20 or 62.8 per cent showed spike and wave activity. (Two 25 year old iden-

TABLE 2
PER CENT ACTIVATION ACCORDING TO AGE

Age	*Total*	*Positive activation*	*Negative activation*
NORMAL CONTROLS			
Under 30	59	32 (54.2%)	27 (45.8%)
Over 30	61	10 (16.4%)	51 (83.6%)
EQUIVOCALS			
Under 30	28	16 (57%)	12 (43%)
Over 30	53	22 (41.5%)	31 (58.5%)
DEFINITE CONVULSIVES			
Under 30	14	11 (78.6%)	3 (21.4%)
Over 30	35	27 (77.1%)	8 (22.9%)

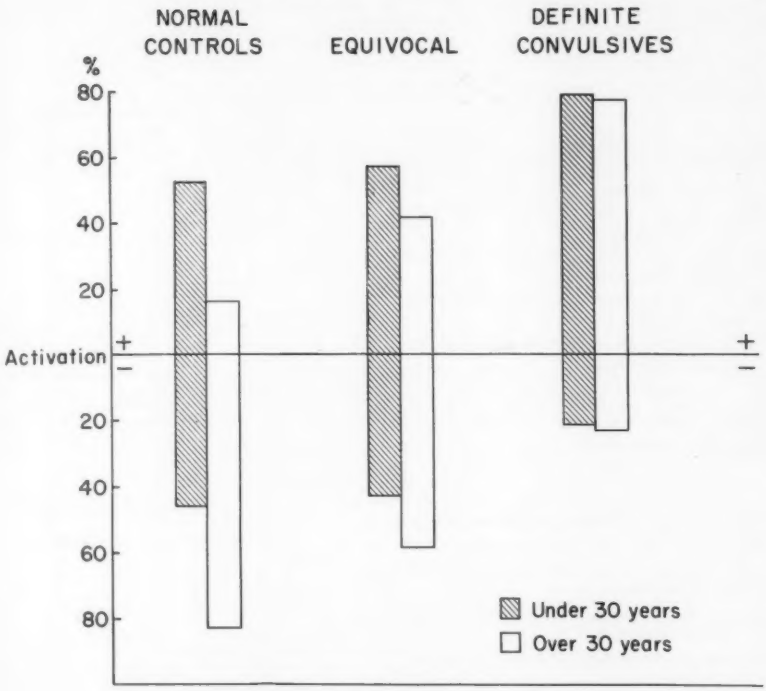

FIG. 1. Influence of age on Metrazol activation.

tical twins with negative pre-Metrazol electroencephalograms showed spike and wave activation at approximately 280 mg. in one and at 300 mg. of Metrazol in the other.) Only one of the ten positive activations in the normals over the age of 30 had spike and wave activity.

The dosage producing spike and wave activation ranged from 200 to 500 mg. of Metrazol, with a mean of 360 mg. This dosage is roughly the same for all kinds of positive activations in all the groups of whatever age.

Fifteen out of the 120 normal individuals had abnormal pre-Metrazol electroencephalograms, which is quite comparable to the percentage found by others in larger series of normals. The influence of the pre-Metrazol record on activation can be seen in table 3 and in figure 2. Of the normals under the age of 30, nine out of 10 with abnormal pre-Metrazol records showed positive activation. Eight of the patients in the entire convulsive group had abnormal pre-Metrazol records (none were diagnostically specific for epilepsy) and seven of these gave positive Metrazol responses. It is to be noted in table 3 that some of the groups are probably not significant with regard to the number of subjects but suggest further lines of study.

TABLE 3
INFLUENCE OF THE PRE-METRAZOL ELECTROENCEPHALOGRAM

	Normal controls	*Equivocals*	*Definite convulsives*
UNDER AGE 30 GROUP			
Abnormal pre-Metrazol electroencephalogram	10	14	2
Normal pre-Metrazol electroencephalogram	49	14	12
Abnormal pre-Metrazol electroencephalogram with activation	9	8	2
Abnormal pre-Metrazol electroencephalogram without activation	1	6	0
Normal pre-Metrazol electroencephalogram with activation	23	8	9
Normal pre-Metrazol electroencephalogram without activation	26	6	3
Total	59	28	14
Positive activations	32	16	11
Negative activations	27	12	3
OVER AGE 30 GROUP			
Abnormal pre-Metrazol electroencephalogram	5	19	6
Normal pre-Metrazol electroencephalogram	56	34	29
Abnormal pre-Metrazol electroencephalogram with activation	2	11	5
Abnormal pre-Metrazol electroencephalogram without activation	3	8	1
Normal pre-Metrazol electroencephalogram with activation	8	11	22
Normal pre-Metrazol electroencephalogram without activation	48	23	7
Total	61	53	35
Positive activations	10	22	27
Negative activations	51	31	8

Out of the 250 patients in our entire series, only 16 were female. It is interesting that only one female had a negative test. This is too small a group to be subject to a careful statistical breakdown, but superficially this did not seem to be related to weight, age, pre-Metrazol electroencephalogram, or the group to which they belonged.

It should be mentioned that, within limits, the weight of the patient did not seem to influence our results with Metrazol activation. This finding is at variance with the assumption made by almost all workers that weight is important. No one has actually tested this concept previously. Figure 3 illustrates the positive response of two individuals, one normal and one a convulsive, who were matched closely with regard to age, weight, sex, and so on. The convulsive individual had a spike and wave activation with 425 mg. of Metrazol and the normal showed multiple spike and wave with only 300 mg.

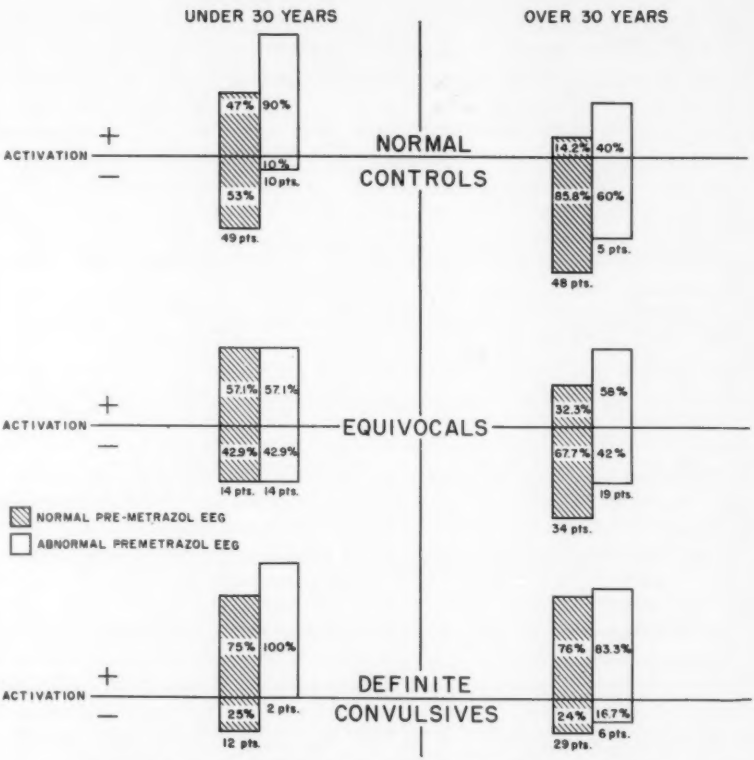

FIG. 2. Influence of pre-Metrazol electroencephalogram on Metrazol activation.

DISCUSSION

Different investigators have used various technics of Metrazol activation for the differential diagnosis of epilepsy. They have reported that the test was diagnostic and specific and that their controls did not activate, or did so in only a small percentage of cases. In purely numerical terms our abnormals gave a percentage of activation comparable to the highest percentage of activation reported in the literature. However, the results obtained in our control group cast doubt upon the widely accepted conclusion that activation, in terms of a generalized paroxysmal response, in a given patient constitutes a valid diagnostic criterion (at least for the diagnosis of epilepsy for the particular technic we utilized).

Apparently an important point which has been overlooked in the evaluation of control groups is the factor of age; no attempt has been made to correlate the percentage of positive responses obtained to the age of the indi-

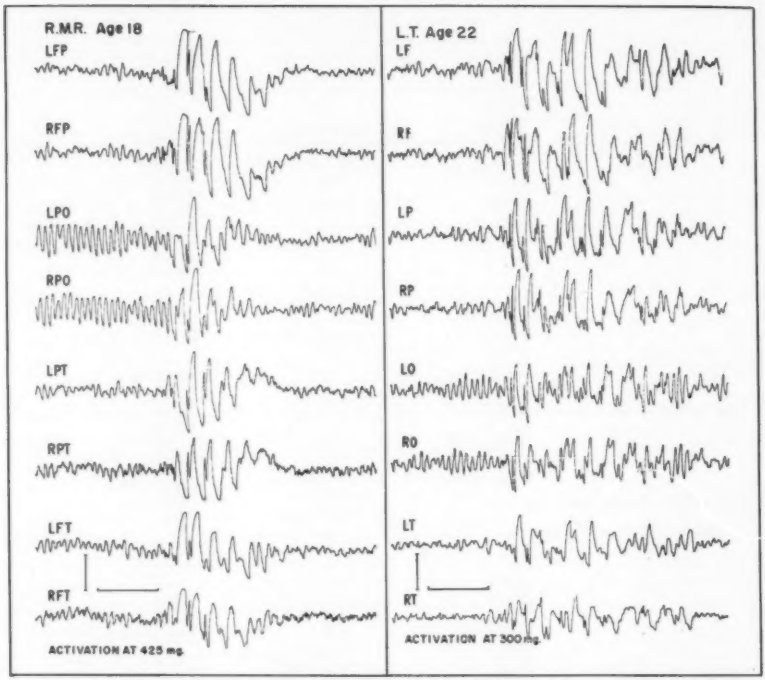

FIG. 3. Positive electroencephalographic response of two individuals, one normal and one a convulsive, matched closely with regard to age, weight, and sex. At left, *R.M.R.*, a white male with grand mal seizures — weight 75 kg. At right, *L.T.*, a normal white male — weight 80 kg.

viduals tested. In discussing the reactivity of convulsive patients to Metrazol, Cure and co-workers[18] spoke of a greater threshold over the age of 40; Renault[19] stated, "the younger are more sensitive." Fuglsang-Frederiksen[23] apparently believed that age is a determining factor in the reactivity of the epileptic subject as he compares the mean age of those who activated (27 years) with those who did not (38 years).

That age is a determinant in the reactivity to Metrazol activation is perhaps not suprising in view of the well-recognized relationship of age to incidence of electroencephalographic abnormalities in general.

It is a documented fact that clinical petit mal epilepsy occurs far more frequently in the individual under the age of 20.[2] The 3 per second spike wave complex is found in over 80 per cent of the records on these patients. With increasing age, clinical petit mal epilepsy becomes much less frequent as does the incidence of the 3 per second spike wave complex in the records of epileptic patients.

Gibbs, Gibbs, and Lennox[17] point out that, "In both normal subjects and those with epilepsy, the incidence of a big build-up (as the response to overventilation) falls abruptly with increasing age until the 35th year, after which the decline is negligible." Thus, age is of prime importance with regard to the incidence of 3 per second spike wave complexes and to the reaction to one type of "activation," namely overbreathing.

The technic used in performing the tests is of unquestioned importance. There are many methods utilized by various groups; thus, generalizations and comparisons of results are often quite difficult. Several investigators[28,29] have reported favorable results with an oral method, but this introduces even more uncontrollable factors in the performance of the test and the interpretation of the results. The intravenous route of injection is most generally accepted. The test is then modified as to dosage and rate of injection. This varies from 20 mg. per 30 seconds to 200 mg. given rapidly intravenously at a single dose. The permutations possible are endless.

The two most common methods are the slow technic, as reported by Merlis and used by us (that is, 25 mg. per 30 seconds), and the fast technic of 2 mg. per kg. of body weight, immediately followed by 1 mg. per kg. each 30 seconds. Jasper[27] has recently modified this with a formula where the rate of injection as well as the total amount is made proportional to the body weight. Various people have assumed that weight is important, but no one has actually compared the percentage of activations with the weight. Within limits, we do not find that weight was important in any of the groups, and this would agree with Ulett[30] and Hutchinson.[22] The slower the rate of injection the less chance of inducing a seizure, which at least makes the test more pleasant for the patient. There also seems to be general agreement that the slow method is more likely to reveal focal changes, but on the other hand, there has been objection to this method on the basis that it does not give high enough percentage of positive results in the entire convulsive group. However, our results would not support this contention.

At this point we are confronted with the problem of specificity, that is, the delineation of normal from abnormal. The slow method is excellent for activating focal abnormalities; but our results would indicate that when the response is generalized it is not diagnostically specific. Buchtal's[26] work would suggest that the fast technic may be more discriminating.

Although the results to be described on the following patient are not in themselves conclusive and will need to be repeated in other patients, they suggest that, within limits, positive activation is dependent upon the individual and not the technic. A 21 year old colored male, weighing 170 pounds, with a clinical diagnosis of plantar wart, and with a negative family personal history for convulsions or any related symptoms, was tested with Metrazol on three separate occasions with three different technics to be described. With the present technic of 25 mg. per 30 seconds, spike and wave bursts were produced by 200 mg. Metrazol (3 minutes 30 seconds), and such discharges could be elicited at will with small increments of the drug. With the so-called "fast"

technic of 50 mg. per 30 seconds, similar spike and wave activity was evoked at 300 mg. of Metrazol (3 minutes 10 seconds). With the technic recently described by Jasper[27] as the standard procedure used in his laboratory (which in this patient consists of giving 1 ml. every 30 seconds of a solution containing 75 mg. per cc.) spike and wave activity was produced at a dosage of 225 mg. (105 seconds); when another increment of 75 mg. was given, spike and wave activity continued to appear intermittently during the next four minutes.

These findings suggest that, regardless of the technic used, paroxysmal spike and wave patterns can be produced with a low dosage of Metrazol in an individual with a negative history for convulsions, negative family history, and no related symptomatology. An attempt is now being made to test more than one technic on all normal subjects showing positive responses to Metrazol activation.

Metrazol threshold as suggested by Ziskind and others [31,32] is subject to so many unknown and uncontrollable variables as to make it clinically useless.

The make-up of the various control groups reported in the literature is interesting. Normal is most often defined as the absence of seizures. The majority of controls were psychiatric patients and the positive results as a whole were low. On the other hand, with some technics the highest percentage of activation reported in the literature was obtained in psychiatric patients. Hutchinson[22] reported that ten patients suffering from conversion hysteria showed positive responses. Cohn[8] obtained over 50 per cent activations in a group of individuals with narcoleptic and aggressive clinical behavior. Browne-Mayers[25] found quite a high percentage of so-called positive tests in neuropsychiatric patients with abnormal "epileptoid" pre-Metrazol records. Our selection of normals was very rigid and included only a very few cases (11) who were subsequently discharged with a psychiatric diagnosis.

Sex differences are usually not mentioned, but Cure[18] found no difference. In the convulsive group, everyone seems to agree that an abnormal pre-Metrazol electroencephalogram greatly increases the chances of a positive test. Most investigators found a higher percentage of activation in individuals with frequent seizures, but Merlis[20] did not find this to be true.

It is well known that convulsions can be induced in anyone with appropriate stimulation. The assumption has been made that there is a group ("epileptics") with an increased susceptibility, that is, with a low threshold of activation. Furthermore, the classic 3 per second spike and wave pattern has been almost universally accepted as a sign by which the epileptic may be differentiated from his normal brother. Yet, by the use of Metrazol, spike and wave can be elicited in a high percentage of normal controls as well as in epileptics and with little correlation in regard to threshold. The spike and wave pattern is apparently elaborated by a mechanism which many of us, perhaps all, possess; why some have seizures and others don't would appear to be due to something other than the simple ability to produce a certain type of electrical discharge pattern.

In clinical terms we can reduce the discussion of Metrazol activation to

one important question: "Can the test be used for the diagnosis of epilepsy?" Our results suggest that this answer must be both "yes" and "no" – it seems to be diagnostically valid when it gives a focal response, as no such responses were produced in our normal group. On the other hand, a generalized paroxysmal response, even when it is a spike and wave pattern, cannot reasonably be considered reliable evidence of a convulsive disorder.

SUMMARY

1. Metrazol activation studies have been made in 250 subjects. Of these, 120 were a highly selected group meeting strict criteria of normality. Eighty-one patients were diagnostic problems with equivocal epileptoid symptoms and/or abnormal electroencephalograms, and 49 were definite convulsive cases having nondiagnostic electrographic findings.

2. Fifty-four per cent of normal controls under the age of 30 gave a positive response, and 62 per cent of these were the spike and wave type. Of 61 normals over the age of 30, 16.4 per cent showed a positive response. Thus, age seems to be an extremely important factor in determining the electrographic response to Metrazol.

3. None of the normal group showed focal abnormalities with Metrazol. The slow technic was, however, very effective in activating focal abnormalities in the abnormal group.

4. These findings are discussed in relation to the problem of the use of chemical activation as a diagnostic technic in clinical electroencephalography. Sex and weight are factors whose influence on the reactivity to Metrazol needs further study.

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Epilepsy may commence in one of three ways. First by minor seizures which occur alone for months or years before there are severe attacks. The attacks of *petit mal* are often at first slight and attract little notice, but become more frequent, until suddenly a severe convulsion occurs. The patient and his friends do not associate the two forms of convulsion, and it is always necessary to make careful inquiry for the occurrence of minor seizures, antecedent to that which the patient believes to have been the first epileptic fit. It is common, for instance, for a patient to say that he has had fits for a few months only, when attacks of *petit mal* have been occurring for years.

The second mode of commencement is by severe fits recurring at short intervals, without any preceding *petit mal*. The second fit occurs within a few days or a few weeks after the first, and the attacks recur at short intervals.

The third mode of onset is with a single severe fit, and no other fit or sign of epilepsy for months and even years, when another attack occurs, after which they usually become frequent. Between the last two forms there is every gradation of varying interval between the first and second fit.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

The "False Positive" Lumbar Myelogram

William V. Trowbridge, M.D. and John D. French, M.D.

Of the tests employed to delineate herniations of the spinal intervertebral disks, the Pantopaque myelogram has been generally accepted as the most objective. For such lesions in the cervical region the accuracy of defects in the radiopaque column is consistently high,[1,2] and a normal study in this region has similarly been found to be acceptably accurate.[1] Even so, severe abnormalities of the cervical disks, with compression of the spinal cord, may be present when no major abnormalities are demonstrable in the myelogram.[3]

In recent years the accuracy of the myelogram in cases with lumbar disk lesions has been found to be far from perfect. Although large defects are ordinarily significant, many severe lesions may compress nerve roots in such a position that their presence is not indicated by the contrast study.[4] These "false negative" findings have been commonly considered to constitute the largest source of error in lumbar myelography.[5,6]

Similarly, "false positive" myelograms have been described repeatedly, but much less frequently than the other types of spurious information obtained from such studies. Their incidence has been found to vary in different series between 3.5 per cent[5] and 5.3 per cent.[6] In spite of this low number, it is not uncommon for the surgeon to explore interspaces showing small, suggestive defects at the same time that other regions with massive defects are investigated. This is a logical approach in that the frequent presence of multiple disk herniations is well known, as is the occasional presence of intense disk pathology in a region where myelographic disorders are minimal.[7,8] Often, in such explorations, the area of minimal defect is examined with a total failure to expose any discernible disease. It is probably under such circumstances that the vast majority of "hidden disks" are removed.

The nature of myelography as a diagnostic procedure militates against its use for purely academic purposes. Thus, a large series of myelograms is essentially unobtainable in individuals whose spinal subarachnoid space is known to be clinically normal. The opportunity does arise, however, to survey my-

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elographically the lumbar subarachnoid space of those persons whose clinical disorders are limited to the cervical or high dorsal regions.

In the past two years all persons studied with cervical myelography by the authors have been carefully questioned concerning previous difficulties referable to the lumbar spinal region. From this entire group, 25 individuals were found who denied any history of low back pain, sciatica, or other evidences of lumbar nerve root or cauda equina compression. It is the purpose of this report to present the findings of routine lumbar myelography in this group of 25 patients.

TECHNIC

The standard technic for cervical myelography was employed in all cases. Lumbar puncture was performed at the second or third lumbar interspace, and 6 cc. of Pantopaque were instilled into the subarachnoid space. The oil was moved into the cervical region by gravitation, and following survey of this region was pooled in the lumbar cistern. Prior to removal of the oil, the lumbar region was surveyed fluoroscopically for major defects in the Pantopaque column. In all cases, films were obtained demonstrating the opaque medium at levels of the fourth and fifth lumbar interspaces. At the termination of the study all available Pantopaque was removed by aspiration from the lumbar cistern.

FINDINGS

In all cases the lumbar films obtained by this method were presented to a radiologist for interpretation, without information regarding the presence or absence of clinical signs or symptoms indicative of lumbosacral root compression. The reports obtained in this manner indicated the presence of persistent myelographic defects in 14 of the 25 cases, constituting positive findings in 56 per cent of the entire group. These defects were stated to be "consistent with, or suggestive of, a herniated intervertebral disk" at the appropriate levels. In one instance a large bar defect was found at the level of the lumbosacral interspace (figure 1), but there were no complete subarachnoid blocks demonstrated in this group. In one case there was myelographic evidence of lumbosacral arachnoiditis in such severe form that the oil could not be moved cephalad beyond the twelfth dorsal interspace, prohibiting cervical myelography. In spite of this arachnoiditis (confirmed in the cervical region by surgical exploration), the patient had never suffered any distress referable to the sacral, lumbar, or dorsal areas.

Of the defects encountered in this series, none was at the site of the lumbar puncture, so their presence could not be ascribed to the spinal needle. Seven of the defects were limited to the L-4 interspace and five to the L-5 interspace. In two cases there were defects at both the L-4 and L-5 levels, and in two other patients bilateral defects were present. All of the defects delineated were sufficiently definite that surgical exploration in the region of myelographic disorder would have been undertaken had the patient pre-

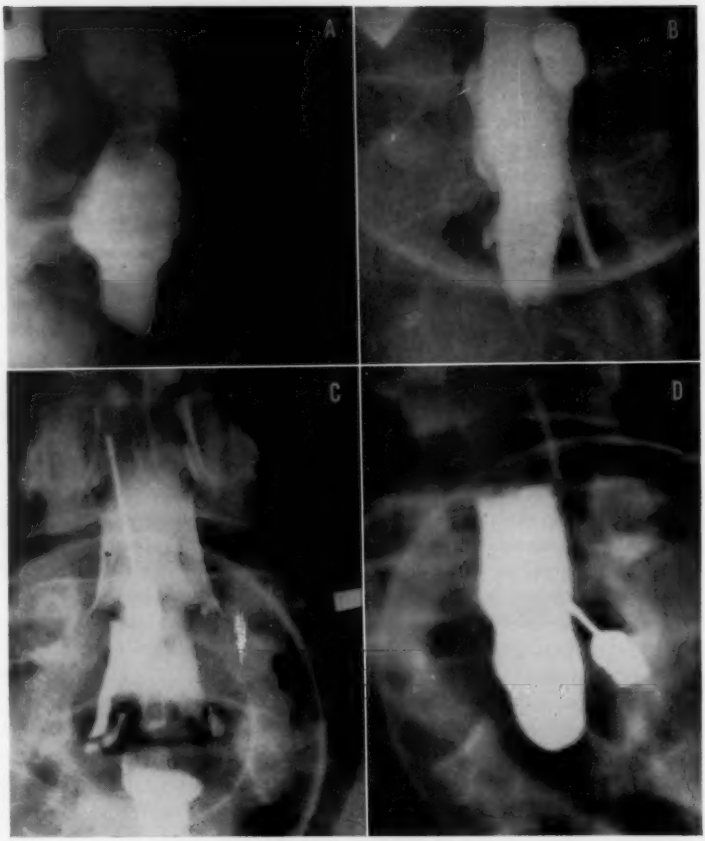

FIG. 1. Lumbar myelograms in four patients with no clinical disorder in this area. *A* and *B* show large indentations of the Pantopaque column. In *C* a large bar defect exists at L-5, while *D* shows a small but definite column indentation at the L-5 level.

sented major complaints of low back or sciatic pain. The abnormalities demonstrated were frequently in the form of an indentation of the Pantopaque column, but more often were seen as deformities or non-filling of the nerve cuffs (figure 1).

DISCUSSION

Designation of these contrast study defects as "false positive" myelograms is admittedly a different use of this terminology than the ordinary connotation. The term, "false positive" myelogram, is ordinarily employed where such defects, in the presence of clinical distress, are unassociated with detectable

disease at surgical exposure of the region. In spite of the ambiguity of terminology, defects such as these are false positives in a clinical sense, since the mechanism producing the abnormality is not of clinical significance. There seems to be little doubt that similar spurious defects may be present in an individual having severe back pain or sciatica.

Although a large proportion of these myelograms revealed defects consistent with nerve root or dural sac compression, it would be fallacious to assume that such a defect is due to artifact. Certainly these defects are representative of some mechanical abnormality which interferes with filling in the particular region visualized. It is entirely conceivable that any of the patients with abnormal lumbar myelograms might develop lumbar or sciatic pain at a later date when these same defects might well be significant. It would not appear necessary for all disk protrusions to cause pain, if their location were such that nerve roots were not encroached upon. Indeed, Wilkinson[9] has noted the presence of profound narrowing of the lumbosacral disk space in over 70 per cent of routine lumbar spine films in persons with no complaints suggestive of intervertebral disk disease. Further evidence that disk ruptures may be painless is provided by Lindblom and Rexed[7] who found that complaints of sciatica or lumbago had been present in the histories of only six of 17 cases showing severe lumbar disk protrusions at autopsy. In all of their cases there was macroscopic or microscopic evidence of nerve root damage from compression. Thus, it is possible that when an individual develops sciatica he may have had a major defect present prior to the onset of distress. In addition, when a defect is present in association with appropriate clinical abnormalities, it is suggested that the basic anatomic disorder may have been present over a protracted period.

The absence of pain with disk disorders is known to occur in the cervical region where advanced disk disease may be quite painless.[4] Such occurrences are probably more common in the lumbar region where the much larger spinal canal could easily accommodate large disk ruptures without concomitant nerve root compression.

In spite of the evidence of anatomic disorder presented by these myelographic defects, it does not necessarily follow that all such defects are clinically significant. The presence of multiple defects in routine lumbar myelography in the disk syndrome is common, appearing in approximately 16 per cent of the lumbar myelograms performed at this institution.[10] It would seem that such multiple defects would seldom be of equal clinical significance. Of two lumbar defects, one might well be of no clinical consequence while the other represents the site of the offending disorder. The problem of myelographic localization is further complicated by the known high incidence of minimal defects at the level of severe, symptomatic disk ruptures.[7,8] It is simple to visualize a situation where a major defect is caused by an asymptomatic lesion, while the offending disk rupture is represented by only a minimal myelographic abnormality.

The presence of such a large number of abnormal studies (56 per cent) in a clinically normal area suggests that false positive myelograms are not uncommon. In the presence of multiple defects it would appear impossible to decide by radiographic methods alone which myelographic abnormality is at the site of the symptomatic lesion. Although single defects would carry a much higher incidence of correct localization, it is possible that such a defect might be of no clinical significance, while the offending abnormality is at a level revealing a false negative pattern.

It becomes obvious that the myelogram requires careful interpretation in the light of clinical findings. In this respect, the radiologist and the neurosurgeon are widely separated in degree of responsibility. It seems implicit that the radiologist be completely objective while interpreting myelograms, describing the Pantopaque column as it appears on the films, since definitive interpretation must rest on the abnormalities elicited in the history and neurologic examination. Without personally conducting a complete historical and physical survey on the patient, the radiologist could hardly be expected to evaluate the significance of myelographic defects. On the other hand, the neurosurgeon would similarly be required to interpret the radiographic abnormalities only in regard to the clinical picture presented by the patient. Under no circumstance should the radiologist's report of a myelographic defect serve as a flat directive to the surgeon that a specific area should be explored. Further, the presence of a myelographic defect does not indicate in any definitive way that conservative treatment would be of no avail. Since the defect may have been present for a protracted period of time with no attendant distress, its continued presence would not necessarily prohibit long periods of remission.

These findings imply that the myelogram should not be the decisive factor in the questionable case, where it has been extensively employed as a criterion for or against surgical exploration.[11,12] In like manner, the use of myelography would seem to be dangerous in those individuals whose findings suggest conversion hysteria, since a radiographic abnormality would conceivably be present in a high proportion of such cases even when no regional pathology is present. By the same token, the medicolegal value of the myelogram is diminished tremendously.

Although the accuracy of the lumbar myelogram is placed in doubt by these findings, the authors wish to emphasize that they still consider such studies an extremely valuable member of the diagnostic armamentarium. When evaluated critically, the myelogram is an important adjunct to the clinical evaluation of individuals suffering from low back and sciatic pain. To suggest the abolition of the myelogram from the study of these cases on the grounds that false positive findings might be present would be as ridiculous as implying that gastrointestinal contrast studies are useless, since the presence of a duodenal bulb deformity is not always of definitive significance in establishing the cause of abdominal pain.

SUMMARY

1. In 25 patients studied with cervical myelography, routine lumbosacral films were also obtained. None of these patients had ever suffered low back or sciatic pain.

2. A total of 14 abnormal lumbar myelograms were obtained in this regionally asymptomatic group, constituting 56 per cent of the total cases studied.

3. These findings suggest that "false positive" myelograms are probably not as uncommon as previously thought.

4. The presence of a defect in the lumbar myelogram does not necessarily indicate the site of a symptomatic lesion.

5. The presence of a lumbar myelographic defect constitutes no assurance that conservative therapy will be unsuccessful.

6. Although it continues to be a useful adjunct to clinical evaluation, the lumbar myelogram should not be used in questionable cases or to establish the presence of an abnormality for medicolegal purposes.

7. The myelogram should be reserved for the study of those cases for whom surgery is contemplated, and even then should be subjected to a critical evaluation in the light of clinical findings.

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Experiences With RO-2-3059 As an Anticonvulsant

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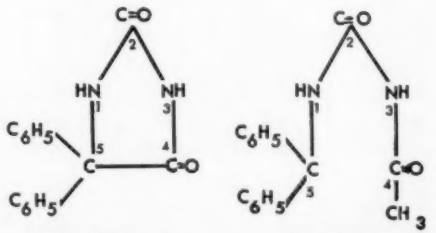
THIS REPORT concerns the use of a new anticonvulsant, RO-2-3059, in the treatment of 43 epileptic patients in the neurology out-patient clinic of the Ohio State University College of Medicine.

CHEMISTRY

The anticonvulsant properties of certain urea derivatives, for example, phenylacetylurea and diphenylhydantoin, have been known for a number of years. RO-2-3059, or 1-benzhydryl-3-acetylurea, represents the first anticonvulsant derived from a hydantoin by opening the ring between positions 4 and 5. This relationship is shown below:



PHARMACOLOGY

In animal tests RO-2-3059 was found to be at least equal and usually greater in activity than diphenylhydantoin or phenylacetylurea in raising the threshold to convulsions produced by minimal electroshock in cats. It was also one-half to one-fourth as active as diphenylhydantoin or phenylacetylurea in protecting rabbits against maximal electroshock seizures. There was very little anti-Metrazol convulsant activity when tested in mice. Very high doses were necessary to produce any neurotoxic symptoms in animals.

From the department of medicine, division of neurology, Ohio State University, Columbus.

TABLE 1

Results of Anticonvulsant Therapy with a Combination of RO-2-3059 and Phenobarbital

RO-2-3059 (500 mg.) with Phenobarbital (45 mg.)

Case	Age	Sex	Age of Onset	Type of Seizure	Etiology	Daily Dosage	Other Daily Medication	Total Dosage	Side Effects	Seizure Incidence (By Months) 1	2	3	4	5	6	REMARKS
1.	20	M	12	GM, PM, TL	Traumatic	1500 mg.	Mesantoin 200 mg. Thephorin 100 mg.	270 gm.	Minimal hand tremor	0	0	3 PM	0	2 PM	0	Working regularly. Best control ever.
2.	41	M	19	TL, GM	Traumatic	1250 mg.	Phenobarbital 45 mg.	225 gm.	None	7 TL	8 TL	7 TL	8 TL	5 TL	8 TL	Attacks usually last less than a minute. Wife feels he would have many more if he were not on prescription.
3.	43	F	41	TL, GM	Neurosyphilis	750 mg. (2 mos.), 1000 mg. (4 mos.)	None	165 gm.	None	1 GM 1 TL	4 TL	3 TL	3 TL	6 TL	6 TL	All attacks last less than one minute.
4.	18	F	12	GM	Traumatic (?)	750 mg. (1 mo.), 875 mg. (5 mos.)	None	155 gm.	None	1 GM	0	0	0	1 GM	0	Feels well, working regularly.
5.	44	M	11	TL, GM	Unknown	1500 mg.	Phenobarbital 100 to 150 mg.	270 gm.	Possible slight euphoria	1 TL	4 TL	2 GM 1 TL	2 TL	1 TL	0	Has worked regularly. (N.B., Patient later died in traffic, possibly due to a convulsion.)
6.	18	M	7	GM	Unknown	1000 mg. but irregular	None	142 gm.	Moderate tremor	2 GM*	0	1 GM*	1 GM	1 GM	0	Patient has cooperated poorly.
7.	31	M	12	GM, PM	Traumatic	750-1250mg. (mostly 750)	Mesantoin 200 mg. (first month only) Mebaral 300 mg. Amphetamine 20 mg.	140 gm.	None	2 GM 100 PM	3 GM 8 PM	6 GM 40 PM	4 GM 90 PM	0 GM 15 PM	0 GM 3 PM	When not on medication, will have 1-4 GM and 10-50 PM attacks a day. Has tried all available drugs without success.
8.	32	F	10	GM	Unknown	500 mg.	None	65 gm.	None	0	0	0	1 GM*	0	0	Good control.
9.	40	F	23	TL	Traumatic	1000 mg.	Dilantin 100 mg.	170 gm.	Probably none. Had depressed WBC for 6 weeks with "spontaneous" improvement.	0	0	0	?	8 TL*	0	Quit medication and had 8 attacks in a few days time. Resumed prescriptions and attacks ceased.
10.	23	M	2	PM, GM	Traumatic	1000 mg.	None	170 gm.	None	6 PM	9 PM	5 PM	13 PM	4 PM	5 PM	Attending school regularly, well satisfied.
11.	20	M	14	GM	Unknown	1250-1000 mg.	Mesantoin 300-500 mg.	177 gm.	None	0	1 GM	6 GM (Jack.)	*7 GM	0	0	Quit medication at time of an attack of "flu" and had series of 7 GM seizures.
12.	43	M	42	GM	Cerebral Vascular Accident	750 mg.	None	128 gm.	None	0	0	0	0	0	0	Employed regularly.
13.	25	M	24	GM	Traumatic	1000 mg.	None	170 gm.	None	GM	0	0	0	0	0	Had "35-40" attacks in year before starting treatment.
14.	42	F	41	TL	Neurosyphilis	750 mg.	None	128 gm.	None	5 TL	7 TL	7 TL	10 TL	8 TL	8 TL	Does not take medication regularly. Indulges in beer-drinking at times. Feels remarkably well; formerly had 25-50 attacks a month.
15.	27	F	4	GM	Unknown	750-1000 mg.	Dilantin 300 mg.	150 gm.	Slight euphoria	0	0	1 GM	0	0	0	Had only fair control on 600 mg. Dilantin and 150 mg. phenobarbital. Also was quite dull and ataxic on those medications. On this routine has been more alert. Excellent control.
16.	24	M	13	GM	Traumatic	1000 mg.	Dilantin 100-200 mg.	170 gm.	None	0	0	0	0	0	1 GM	Excellent control. Working regularly.
17.	26	F	16	GM	Neurosyphilis (?)	500-1000 mg.	Dilantin 200 mg.	128 gm.	Slight tremor on 1000 mg. dose	5 GM(L) 1 GM(S)	6 GM(L)	6 GM(L) 1 GM(S)	3 GM(L)	3 GM(L)	3 GM(L)	Had poor control with large doses of other anticonvulsants. Pregnant during months 2-6 of present study.
18.	37	M	30	GM	Neurosyphilis	500 mg.	Dilantin 400-500 mg.	42 gm.	None	3 GM(L)	2 GM(L)	3 GM(L)	2 GM(L)*	2 GM(L) 1 GM(S)*	3 GM(L)	Not very reliable with regard to following directions. His light attacks last only a few seconds.
19.	54	M	35	GM	Neurosyphilis	750 mg.	Dilantin 100 mg. Amphetamine 10 mg.	128 gm.	None	0	0	0	0	0	0	Good control.
20.	22	M	14	GM	Unknown	500-1000 mg.	Mesantoin 100-400 (usually 300 mg.)	125 gm.	Moderate tremor on 1000 mg. dose	2 GM(S) 3 GM(L)	5 GM(S) 3 GM(L)	2 GM(S) 2 GM(L)	9 GM(S)*	3 GM(S)	4 GM(L)	"Adjusted" his medication without doctor's permission. Very maladjusted from social standpoint. Poor hygiene. Stopped RO-2-3059 with phenobarbital for a few days and had 6 GM attacks. Started the medication again and went 28 days without any severe attacks, but had several light, abortive ones.

GM—Grand mal
PM—Petit mal
TL—Temporal lobe

*Admitted missing regular medication before attack.
L—light attack
S—severe attack

PROCEDURE AND CLINICAL OBSERVATIONS

At the outset of the study, RO-2-3059 was given alone. Dosages up to 500 mg. per 50 pounds of body weight were generally well tolerated; above this level certain toxic manifestations appeared. These consisted largely of skeletal muscle tremors and typical psychic disturbances to be described below.

The tremor, evident in practically all of the skeletal muscles, was most easily demonstrated in the limbs, especially in the hands. Periods of exacerbation, described by one patient as "surges" were characteristic of the tremor. Involvement of the speech musculature gave rise to a disturbance closely resembling stuttering. In one individual the tremor of the head and eyes made it virtually impossible for him to read; because of a forceful tremor in the hands he was also unable to write.

Of greater concern from the standpoint of side effects were symptoms of excessive central nervous system stimulation, manifested in most instances by a feeling of being "keyed-up" and by inability to concentrate. In three cases these disturbances were so marked that the subjects, considered by some observers to be psychotic, were detained for a brief period on a psychiatric ward.

In an attempt to eliminate these undesirable effects, RO-2-3059 was tried in combination with phenobarbital. It was soon evident that the combination had the therapeutic virtues of the benzhydryl compound, with little of the side effects which had resulted from its use alone. Tablets containing 500 mg. RO-2-3059 and 45 mg. phenobarbital were used. The combination has been used in a total of approximately 40 patients, about half of whom failed to continue follow-up visits and have been eliminated from the study. The remaining 20 patients have been under treatment for from two to three years. The RO-2-3059 and phenobarbital combination has been in use during the over-all period.

There has been ample opportunity to vary the dosage, to use other anticonvulsants concomitantly or alternately, and to observe the effects upon the seizure pattern produced by temporarily withholding the medication. Although a number of the 20 patients included in the study have been under treatment with the combined drugs for from two to three years, detailed observations will be described only for the period of six months prior to preparation of this report. The essential details of history, physical findings, dosage, and results are summarized in table 1.

The patient group consisted of 13 males and seven females, ranging in age from 18 to 54. The age at onset of the convulsive disorder for the entire group varied from two to 41 years. Twelve had grand mal seizures, two had temporal lobe attacks, three had mixed grand mal and temporal lobe episodes, two displayed a combination of grand mal and petit mal, and one had all three types of seizures. The etiology was considered to be traumatic in seven, possibly traumatic in one, idiopathic in six, neurosyphilitic in four, and possibly

neurosyphilitic in another; in one subject the convulsive disorder was attributed to a cerebral vascular accident. Twelve patients had not been well controlled by other anticonvulsant medication prior to the use of this new preparation. The daily dose of RO-2-3059 for the entire six month period varied from 500 mg. to 1500 mg. Twelve used RO-2-3059 and phenobarbital in conjunction with other anticonvulsants. Two of these were given 10 or 20 mg. of amphetamine sulfate in addition, and one received regular daily doses of an antihistamine, Thephorin. Two patients took daily supplementary doses of phenobarbital (beyond that in the combination tablet) of from 45 mg. to 150 mg.

Eight patients used only the combination preparation in the usual ratio of 500 mg. RO-2-3059 to 45 mg. phenobarbital. In this group, seizure control was rated as good in three cases and excellent in five cases. Of the 12 individuals who were given other anticonvulsants or supplementary doses of phenobarbital, the control was regarded as poor in one, fair in two, good in seven, and excellent in two. Examination of table 1 shows several instances in which discontinuance of the medication signaled resumption of attacks. This sequence of events had been observed frequently during the two years or so prior to the six month period covered by this report.

One of the most striking observations during treatment with RO-2-3059 and phenobarbital was the sense of well-being and euphoria frequently recounted by the patients. This is in marked contrast to the depressed or retarded state commonly encountered with other anticonvulsants. In many instances patients could be described as alert, active, and ambitious. Social adjustment was good in every case but one, and five who had not worked before taking the preparation subsequently obtained regular employment. The only side effect observed from the combination of RO-2-3059 with phenobarbital was nervousness when a large dosage was given. Minimal to moderate hand tremor was reported in three patients, all of whom were on daily doses of at least 1000 mg. RO-2-3059. There was no abnormality of the gums and no involvement of the skin. All patients in the series had complete physical examinations and white blood counts. There were no abnormal physical findings that could be attributed to the use of the combination preparation. One patient showed moderate leukopenia for six weeks but the role played by the medication was obscure; leukopenia disappeared spontaneously despite continuance of the drug.

SUMMARY AND CONCLUSIONS

RO-2-3059, a new benzhydryl derivative with anticonvulsant properties, has been used alone and in combination with phenobarbital in 43 patients in the neurology out-patient clinic of the Ohio State University College of Medicine. These were comprised of patients with grand mal, petit mal, and temporal lobe seizures, singly or in combination. A combination of RO-2-3059 with phenobarbital was chosen for continuing therapy in approximately

40 of these, in view of symptoms suggesting excessive central nervous system stimulation when RO-2-3059 was given alone. Of the original group of patients so treated, 20 have continued follow-up observation; this report covers the details of treatment and observations for the preceding six months. In eight patients of this group, the RO-2-3059 and phenobarbital combination was the sole anticonvulsant agent; the remaining 12 received one or more additional anticonvulsants or supplementary doses of phenobarbital as adjunctive therapy. The observations included repeated physical examinations and blood counts; in several instances the effects of discontinuing medication temporarily were also determined.

In general, RO-2-3059 combined with phenobarbital was found to be moderately effective against grand mal seizures, rather ineffective against temporal lobe attacks, and relatively ineffective or perhaps worthless against petit mal attacks. Side effects were mild even at high dosage levels, and consisted chiefly of nervousness, low amplitude muscle tremors, and euphoria; this last feature was considered in most cases as more of an advantage than otherwise.

On the basis of limited experience to date, RO-2-3059 in combination with phenobarbital is considered worthy of more extensive study.

RO-2-3059 supplied for clinical trial by Dr. R. J. Floody, Hoffmann-La Roche Inc.

We have still too little definite knowledge of the intimate pathology of epilepsy to permit safe generalization regarding the possible mode of action of the several drugs which are found, clinically, to be useful. All that can be done is to recognize the kind of action which they have been found, by experiment, to exert upon the nervous system.

The character of the cases in which this or that drug is especially useful, *i. e.*, the "indications" for special treatment, is a subject of the greatest practical importance. There is no point in therapeutics, however, more open to fallacy, or on which more generalizations have been published which subsequent observation has proved to be inaccurate. No disease baffles more completely the therapeutic investigator. Of two cases that seem essentially similar, one is influenced by a drug that has no effect whatever on the other. While pointing out, therefore, when possible, the class of cases in which this or that method of treatment has seemed most useful, I have thought it better to illustrate the effect of remedies by the brief narration of some cases in which that effect was well marekd, rather than to formulate a series of precise "indications" which experience might fail to confirm. The cases described are selected from a larger number, as those which seem most instructive.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases,* published in 1885.

Spontaneous Rhythmic Ocular Movements

Their Possible Relationship to Mental Activity

Harry A. Teitelbaum, M.D., Ph.D.

SPONTANEOUS RHYTHMIC EYE MOVEMENTS of a nystagmoid nature have been observed in patients undergoing psychotherapy. These eye movements have also been noted in almost all other people observed, occurring most commonly when the subjects under scrutiny sat in silence in mental concentration with eyes gazing into space, or when they paused for variable periods of time in the course of speech. At first it appeared that these rhythmic eye movements had a very specific relationship to mental concentration in silence, when the eyes looked into space. However, on further study, they were observed in some subjects while they were talking, and also while their eyes were fixed directly on those of the observer.

These eye movements occurred most commonly in the horizontal plane. In one instance they did occur in the vertical plane, and in one they were rotatory, with a counter-clockwise motion. The movements were found to vary in character from person to person, being of different degrees of coarseness, better or more poorly sustained, and more or less constant in appearance. In any particular person, however, the pattern of eye movement did not vary a great deal.

Because there appeared to be some relationship between these ocular movements and the attitude of silent concentration, the frequency of their occurrence during silence as well as during speech was studied. The findings are summarized in table 1. The occurrence or absence of the eye movements during silence in three different attitudes was determined: 1) with eyes gazing into the distance; 2) with eyes fixed on an object, usually the observer's eyes; 3) during momentary pause in speech. The presence or absence of rhythmic eye movements while the subject was talking was observed in two different attitudes: 1) with eyes gazing into the distance; 2) with eyes fixed on an object.

Seventeen subjects in the study were tested for nystagmus. Only one, No. 7, had transitory nystagmus on lateral gaze to either side. These subjects had no clinical neurologic or ophthalmologic disease. That the eye movements under consideration here are not related to any pathologic process is

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TABLE 1

INCIDENCE OF RHYTHMIC EYE MOVEMENTS DURING VARIOUS ATTITUDES IN SILENCE AND SPEECH

			Rhythmic Eye Movements During Silence		*Rhythmic Eye Movements While Talking*			
Group	*No.*	*Sex*	*Eyes gazing into distance*	*Eyes fixed on object*	*Momentary pause*	*Eyes gazing into distance*	*Eyes fixed on object*	*Test for nystagmus*
A	1	F	rem(inc.)sm	rem(inc.)sm	rem(inc.) sm	rem(inc.)sm	rem(inc.)sm	neg.
	2	F	rem	rem	rem	rem	rem	neg.
	3	F	rem	rem	rem	rem	rem	neg.
B	4	M	rem(rot.)	rem ?	rem(inc.)	no rem, sm	no rem, sm	neg.
	5	M	rem	rem	rem	no rem, sm	no rem	neg.
C	6	F	rem	no rem	rem	rem(inc.)sm	no rem	neg.
	7	F	rem(inc.)	no rem	rem	rem(inc.)	no rem	pos.
	8	M	rem	no rem	no rem	rem	no rem	neg.
	9	F	rem(inc.)	no rem	rem	rem(inc.)	no rem (occ.jerk)	neg.
D	10	F	rem(inc.)sm	no rem	rem	no rem, sm	no rem, sm	neg.
	11	F	rem	?	rem	no rem, sm	no rem	neg.
	12	M	rem(inc.)	no rem	rem(inc.)	no rem	rem	neg.
	13	M	rem(inc.)sm	no rem	rem(inc.)	no rem, sm	no rem	neg.
E	14	F	rem(inc.)sm	no rem, sm	no rem, sm	no rem, sm	no rem	neg.
	15	M	no rem (occ.jerk)	no rem	rem(inc.)	no rem	no rem	neg.
F	16	F	no rem, sm	no rem	no rem	no rem, sm	no rem	neg.
	17	F	no rem	no rem	no rem	no rem	no rem, sm	neg.
	18	M	rem	?	rem	no rem, sm	?	?
	19	M	?	?	rem	? sm	?	?
	20	M	rem(v)sm	?	?	?	?	?
	21	M	no rem	?	?	?	?	?
	22	F	no rem	?	?	?	?	?

rem—rhythmic eye movements
(inc.)—inconstant
sm—searching movements
(rot.)—rotatory
(v)—vertical
(occ.jerk)—occasional jerk of eyes

further supported by their presence in a very high percentage of people observed.

If the three attitudes during silence and the two during speech are not segregated, the rhythmic eye movements occurred during silence in 15 of the 17 subjects and during speech in only seven of the 17 subjects, as shown in table 2. Considering the various attitudes separately, during silence, with the eyes gazing into the distance, eye movements occurred in 14 of the 17 subjects; with the eyes fixed on an object, in six of the 17 subjects; and during momentary pause in speech, in 14 of the 17 subjects. During speech, with the eyes gazing into space, the eye movements were present in seven of the 17 subjects; with the eyes fixed on an object, in only three of the 17 subjects. It thus appears that with the eyes fixed on an object, these rhythmic movements occur much less frequently both during silence and speech than when the eyes are gazing into space. Also, these eye movements occur less frequently during speech than during silence whether the eyes are gazing into the distance or fixed on an object. One wonders if talking and visual object fixation inhibit these rhythmic ocular movements. If so, these are not the

TABLE 2
OCCURRENCE OF RHYTHMIC EYE MOVEMENTS IN 17 SUBJECTS

Rhythmic Eye Movements During Silence — 15 of 17			*Rhythmic Eye Movements During Talking* — 7 of 17	
Eyes gazing into distance	*Eyes fixed on object*	*Momentary pause*	*Eyes gazing into distance*	*Eyes fixed on object*
14 of 17	6 of 17	14 of 17	7 of 17	3 of 17

only inhibiting processes, for the movements were not present in two subjects, Nos. 16 and 17, either during silence or speech.

In table 1 the 17 subjects with full data available are divided into six groups. Group A consists of three subjects in whom rhythmic eye movements were present in all five designated attitudes during silence as well as during speech. Group B comprises two subjects in whom eye movements were observed during the three attitudes in silence but not during the two in speech. One of these subjects had rotatory eye movements. In group C, with four subjects, eye movements were found in two attitudes during silence and in one during speech. In group D, also consisting of four subjects, eye movements were found in two attitudes in silence and in none during speech. In group E, with two subjects, eye movements were found in one attitude in silence and in one during speech. In group F, also with two subjects, no eye movements were observed in any of the attitudes.

There were five additional subjects on whom observations were incomplete. In No. 18 the eye movements observed were very gross. They occurred during momentary pauses while addressing a class. During pauses the subject gazed off to the side and up towards the ceiling. In subject 19, eye movements occurred during momentary pauses while reading. Subject 20 was the only one with vertical eye movements; these occurred while listening to subject 18 lecture. Subjects 21 and 22 sat during the same lecture with gaze fixed ahead but with no eye movements. They appeared to be rather sleepy. Rhythmic eye movements have also been observed in many other people in various attitudes.

DISCUSSION

It is well known that concentration of perception through any one sense, as through vision during reading, tends to interfere with perception through other senses, such as auditory or tactile. This results from lowering of the threshold for vision and elevation of that for other senses. Adrian[1] refers to this process as "one of the most important factors in perception, namely, the way in which attention is directed. The brain may be wide awake, but if we are looking at something interesting, we may be quite unaware of noises which are certainly sending messages into the auditory area." Also, in abstract concentration, exclusive of the use of any of the various senses, there is interference with perception through all of the senses. A person in deep mental concentration is referred to as "lost in thought." He is relatively non-

responsive to stimuli in his environment. Such a person may automatically hold his hand to his forehead and cover his eyes. He may even close his eyes. Isolation and a quiet environment are often sought by people who have to concentrate on what they are doing. They do not depend entirely on their natural abilities to exclude stimuli by elevation of thresholds.

The person involved in the process of mental concentration may seem to fix his gaze as though he were looking at some particular point. Actually, at such times, there is no visual fixation on any object. The rhythmic eye movements that develop at such times are not comparable to "fixation nystagmus," as described by Walsh.[2] This results from "fixing the eye intently upon some object at rest." Fixation nystagmus is rare, according to Luhr and Eckel,[3] but Walsh believes it "cannot be considered uncommon." Since the ocular movements described in this paper are common, they are not the same as those referred to by Luhr and Eckel. Also Walsh stated that, "Often the oscillation of the eyes originates in abnormalities of ocular fixation and from defective orientation in space, but in many instances the etiology is unknown." Since there is usually no precise visual object fixation in mental concentration, it may be poor ocular fixation that gives rise to the nystagmus, as mentioned by Walsh.

If exclusion of perception through the various sensory channels is important in the facilitation of mental concentration, then a process that interferes with precise focusing of one's eyes could be considered helpful in such concentration. Brickner[4] reported oscillopsia in patients with nystagmus. This involves blurring of vision with the object seeming to move about. Nathanson, Bergman, and Bender[5] showed that nystagmus caused visual disturbances, with diminished acuity and oscillopsia on direct forward gaze.

Recently Aserinsky and Kleitman[6] described rapid eye movements during sleep which they felt might serve as objective indications of dreaming. In a similar sense the rhythmic eye movements reported above could possibly serve as an objective indication of mental concentration. It is not unlikely that the mental processes involved in dreaming and in waking concentration have rhythmic eye movements associated with them, based on the same physiologic mechanism. Aserinsky and Kleitman[6] correlated the electrical activity of the eye movements in dreamers with their electroencephalograms.

Among artifacts that are recorded in the electroencephalogram Schwab[7] included muscle discharges, which could well include nystagmus. In addition, Schwab pointed out, "The potential difference between the cornea of the eye and the retina is a direct current, and the condenser-coupled electroencephalographic amplifiers would not respond to it, but when a direct current field is moved, as during eye blink or nystagmus, the fields become alternating and are picked up by the electroencephalogram recorder. Eye movements are avoided by fixation or by either a technician or the patient's gently holding a pad over them." Thus, nystagmus produces a detectable effect in the electroencephalogram, but since object fixation eliminates such effect, the nystagmus

could not very well be associated with such fixation. This would again indicate that the directed gaze during which rhythmic ocular movements occur in mental concentration is not ocular fixation on a particular object.

Electroencephalographic studies in conjunction with the recording of the likely interferences caused by the rhythmic eye movements described should be able to check the suggested correlation observed between mental concentration and these rhythmic eye movements. Adrian[1] emphasized the well established fact that, "an unexpected touch or sound will banish the (alpha) rhythm momentarily and any mental activity involving concentrated attention will do so, . . . " The alpha rhythm "does not disappear unless our attention is engaged by what we see." Brain[8] pointed out that "the exercise of (visual) imagination interferes with the alpha rhythm, which is regarded as indicating a state of rest in the visual cortex."

In a recent paper, Teitelbaum[9] stressed the significance of beta waves as manifestations of "greater cerebral activity," or of the integrative activity of the cerebrum, while alpha waves represent the resting waking state. Now, since mental concentration gives rise to beta waves and since it appears to be associated with rhythmic eye movements that can be recorded in the electroencephalogram, it is likely that electroencephalographic studies would show both simultaneously.

SUMMARY

The occurrence of spontaneous rhythmic eye movements is described. Their possible relationship to mental concentration is discussed. It is suggested that these eye movements may lend themselves to further clarification by means of electroencephalographic studies.

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Epidemiologic Investigations of Amyotrophic Lateral Sclerosis

1. Preliminary Report on Geographic Distribution, with Special Reference to the Mariana Islands, Including Clinical and Pathologic Observations

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AMYOTROPHIC lateral sclerosis has recently been reported as highly prevalent on Guam in the Mariana Islands.[1–3] Arnold and associates[1] estimated the frequency among the natives of the island Territory as 100 times greater than that in continental United States. Koerner,[2] after reviewing the literature on amyotrophic lateral sclerosis for the previous 20 years, likewise concluded that incidence of the illness among the Chamorros (based on his survey) was much higher than that for other populations. The disease, as he and as Arnold had noted, "differed little from that described classically." A variety of etiologic possibilities, including trauma, nutritional deficiency, toxins, and infectious agents, were considered, but there was insufficient evidence to identify any as predisposing or precipitating factors; it was noted, however, that a high percentage of the patients "gave a history of similar disease in other members of the family."[2]

Since Guam and nearby islands are small and their populations are rather stable, there seemed to be an unusual opportunity to study the epidemiology of amyotrophic lateral sclerosis in the Marianas and the neighboring islands.

The term "amyotrophic lateral sclerosis" as used here refers to the syndrome in which progressive muscular atrophy, progressive bulbar palsy, or progressive lateral sclerosis, alone or combined, occurs as the first symptom complex and usually progresses so that a combination of two or three of these symptom complexes are present in advanced stages of the disease.

The present investigation, sponsored by the Public Health Service and the Bureau of Medicine and Surgery, Department of the Navy, with the coopera-

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tion of the government of Guam, was started in the summer of 1953 and had as its goal the following:

1. To determine whether the reports of the unusual frequency of the syndrome amyotrophic lateral sclerosis reported for Guam could be confirmed, and if so,

2. To determine whether other populations in the Pacific were also afflicted.

3. To determine if Armed Forces personnel, their dependents, and other non-Chamorros who had lived in the endemic areas became unusually susceptible to the disorder.

4. To study, by suitable statistical methods, the progression of disability and life expectancy among groups of patients with various forms of the disease at onset and among the various population subgroups. Such information would provide "expected" prognostic values for future therapeutic studies.

5. To study the natural history of the disease, including annual and seasonal incidence, the detailed distribution in the Marianas and other Western Pacific Islands, and the population selectivity, that is, rates by age, sex, race, and economic and social status.

6. To study possible etiologic factors. If the high familial incidence reported was verified, to determine, if possible, whether this was due to a genetic basis or to some common environmental factor. An hereditary factor might be disclosed by the customary genetic approach. In searching for a possible environmental factor, data would be obtained from two control groups, one a random sample (normal persons from the same village and matched by groups with patients for age and sex) and the other group consisting of unafflicted siblings of patients (preferably older and of the same sex).

As of the present writing, the first five aims have been partially fulfilled.

Soon after our arrival on Guam it became obvious that the incidence of a classic form of amyotrophic lateral sclerosis was exceedingly high, as had been reported. In the time available for the preliminary study, it seemed most profitable to determine the geographic limits of the disease and to locate as many patients as possible on the islands in which the incidence was high. The intensive epidemiologic and genetic studies were postponed, and only a brief history of present illness, previous infections, or traumatic episodes and a brief family history were obtained from the patients at this time.

The populations of Guam, Rota, and Saipan in the Mariana Islands* and Moen Island in the Truk Archipelago were surveyed for suspected and diagnosed cases. Additional information was sought regarding any unusual occurrence of amyotrophic lateral sclerosis in other islands in the Western Pacific, including the Philippines and Japan (figure 1).

*The Chamorros constitute the principal population of the Mariana Islands, of which Guam is the largest and southernmost. It is believed that the Chamorros originally migrated from the mainland of Southeast Asia. Following the Spanish Conquest, during the eighteenth century, there was intermixture with the Spanish and Filipino soldiers, so that today most of the "natives" represent a mixed racial origin.

FIG. 1. Map of the Pacific area.

METHOD OF STUDY: CASE-FINDING

The following case-finding methods were employed in the Mariana Islands and on Moen Island:

1. In each village the public health nurse, village commissioners, and, where convenient, the local priest and volunteer social workers were interviewed. The disease was described and all patients suspected or known to have the disease were then examined.

2. Where no cases of the disease were found by this method, mass surveys of the populations were attempted. A brief screening examination of large groups of people was carried out as follows: a) the muscles of the hands and arms were examined for gross weakness or atrophy; b) the tongue was studied for weakness, atrophy, or fasciculations; c) the gait was observed; d) the clarity of the speech was studied as the patient recited several words. Suspected neurologic cases were then examined thoroughly.

3. All patients seen by Koerner, by Tillema, and by Arnold, who had kindly provided all their original case reports, were followed. Those still living who could be visited were examined; hospital records and death certificates were sought for those who had died.

4. The records of all cases of chronic neurologic disorders other than syphilis of the central nervous system (which, incidentally, appears to be rare on Guam) seen in the local hospitals since 1945 were reviewed and the patients were examined wherever possible.

5. All death certificates available were examined, and where deaths were suspected of being due to amyotrophic lateral sclerosis the certificates were copied. Certificates for recent deaths in which diagnostic confirmatory clinical records were not available were traced and family members were requested to provide a history of the case.

On *Guam*, all but the second step were adopted. The principal sources of data on new cases were the local public health nurse and village commissioners, since they were acquainted with "lytico" or "paralytico" which are the terms commonly used by the natives for this disorder.

The records obtained from Tillema were principally those of patients seen at the Guam Memorial Hospital during the previous three years. The U. S. Naval Hospital records in all neurologic diagnosis groups other than syphilis of the central nervous system were reviewed, and an attempt was made to locate all patients suspected of having amyotrophic lateral sclerosis at the time of discharge from this hospital. All neurologic records in the diagnostic files of the Guam Memorial Hospital for the period 1952 to 1953 were also reviewed for other suspected cases. (Incidentally, no cases of multiple sclerosis were located at the U. S. Naval Hospital, and two at the Guam Memorial Hospital diagnosed as multiple sclerosis were found to have no signs or symptoms compatible with such a diagnosis.)

By a most fortunate circumstance, the volumes containing the death certificates for the period 1901 to December 6, 1941, had not been destroyed during the Japanese occupation and these proved to be a valuable source of information.

On *Rota*, amyotrophic lateral sclerosis, here also known as "lytico," was recognized by members of the community. The local medical practitioner and the village commissioner were able to present to us most of the suspected patients during our brief visit. Mortality records and hospital records were almost nonexistent. We did not take the time to survey any large segment of the population, although many who had muscular or arthritic complaints were examined.

On *Saipan*, unfortunately, there was no diagnostic file available for the hospitalized patients from 1945 to the present. Prior to 1945, Saipan was under Japanese control and no medical records for this period were found. Death certificates, which included a brief clinical summary, were available for all years after 1945. The U. S. Navy physicians on duty at the hospital, all the assisting medical practitioners, and the various village leaders as well as the priest on the island were interviewed regarding the occurrence of chronic neurologic disorders, and one of us (Mulder) later examined all suspect neurologic cases as well as a large segment of the Chamorro and Carolinian adult population.

On *Truk*, the civil administration was under the Trust Territory Office of the Department of the Interior. There was no diagnostic file for hospital patients, and death certificates were unavailable prior to 1950. For the period 1951 to the present, the chief of staff of the hospital was able to supply the necessary mortality information.

Since the disease was unrecognized in the Truk population by the medical staff of the hospital or by the village leaders, about 300 adults who could be located either in the hospital or at the specially called assemblies in each of several villages on Moen Island were examined.

METHOD OF EXAMINATION OF SUSPECTED CASES

Wherever possible, each patient was first examined at his home. As complete a neurologic examination as seemed indicated was carried out. All available records on the patients who had been hospitalized were reviewed and laboratory data were abstracted. Several new patients were admitted to the hospital for special laboratory studies, including muscle biopsy and cerebrospinal fluid examination.

COLLECTION OF POSTMORTEM SPECIMENS

Arnold and associates[1] had noted that "the microscopic examination of the spinal cords and brain stems which were secured in seven of the deceased patients confirmed the diagnosis of amyotrophic lateral sclerosis." It is understood that Arnold and Bailey[4] intend to present a detailed report of the findings of these and three more recent cases in the near future. We were able to secure specimens of the central nervous system of two other deceased patients and have briefly presented the microscopic findings.

RESULTS

Clinical observations. Clinically, the syndrome observed on Guam and Rota is amyotrophic lateral sclerosis, as described in detail by Arnold and associates[1] and by Koerner.[2] The typical involvement of the central nervous system as detected by physical examination was essentially limited to the motor system in the forms of muscular atrophy, lateral sclerosis, and bulbar or pseudobulbar palsy. All patients seen had clinical manifestations in at least two and usually more of these loci. Signs of a progressive muscular atrophy were present in all but one patient in our series of 46 cases (42 on Guam and four on Rota). Bulbar involvement was noted in about 75 per cent of the cases; signs of involvement of the corticospinal tracts were also evident in about 75 per cent of the cases (not necessarily in the same patients). Koerner had noted pseudobulbar palsy signs, based on the presence of a sucking reflex, hyperactive jaw jerk, or uncontrollable laughing or crying in 80 per cent of cases. We also noted such findings in most of our cases.

A precise history of onset or a description of the course of the illness was frequently difficult to obtain. Most of the patients whom we saw did not speak English well nor did we understand Chamorro; thus, the interpretation of some terms by English-speaking natives might not have been exact. Furthermore, many patients had advanced disease and in a large proportion of them dysarthria was marked. Most patients could not recall the month or even the season of onset and some were not certain of the year.

As well as could be determined, the site of presenting symptom of weakness or discomfort was as follows:

	Per cent
Upper extremity	57
Lower extremity	17
Upper and lower extremity	9
Bulbar or bulbar with involvement of an extremity	17
	100

The most frequent symptoms noted at onset were numbness and weakness of muscles of the extremities (most often in the hands), and this was usually accompanied by muscle atrophy and fasciculations. Although about one third of the patients complained of numbness or other vague sensory disturbances, no objective sensory dysfunction was noted. There was also no clinical evidence of mental deterioration or any incoordination which was not apparently due to muscle weakness.

Only a few of the patients whom we examined had been seen by a physician early in the course of their illness. The interval between onset of symptoms and first medical observation usually depended on the severity of the disability; it averaged about 14 months for males and about ten months for females. Consequently, few patients with a relatively pure muscle atrophy or lateral sclerosis alone were found.

On the basis of the history and physical findings, patients were classified as having clinically "certain," "probable," or "possible" amyotrophic lateral sclerosis. We have not attempted to classify the cases according to the clinical form which was manifested at the time of the examination. No obvious difference in the character of the clinical pictures of the living patients from that described by Koerner and by Arnold and associates was noted; furthermore, it seemed that such a classification as "complete," "incomplete," or "atypical" was somewhat artificial since it was dependent on the stage of the illness at the time the patient was observed. In almost all the cases seen by Arnold and associates or by Koerner for whom a later clinical description was available, the Charcot or complete form of the disease had eventually developed.

Of the 46 patients whom we saw on Guam and Rota, 35 were classified as certainly, nine as probably, and two as possibly affected. This gives another indication that we were seeing few patients with early disease, since the reported certainty of diagnosis was more often an indication of the stage of development of the disease than of the degree of doubt as to the diagnosis.

There was no obvious difference in the clinical picture by age for the two sexes. However, a more careful analysis must be done before a definite answer on this matter is obtained.

It is of interest that two of our Guam patients not only had findings of amyotrophic lateral sclerosis but also had some signs and symptoms of parkinsonism. Although the occurrence of both amyotrophic lateral sclerosis and parkinsonism in the same patient might be coincidental because of a similarity of age of onset and the relatively high incidence of the two disorders, we also noted that a syndrome which appeared to be postencephalitic parkinsonism occurred occasionally in siblings of our amyotrophic lateral sclerosis patients. We are not certain whether this is due to chance, whether it may represent a predisposition to neurologic disease on the part of certain families, or whether there may be the same factor responsible for the postencephalitic syndrome which is associated with the development of amyotrophic lateral sclerosis.

According to Arnold and associates,[1] none of their patients had been afflicted by the epidemic of Japanese B encephalitis which occurred on Guam in 1947 and 1948 during their investigation, and only three patients could recall a febrile illness suggestive of encephalitis that occurred during their youth. In those few reported cases in which a syndrome resembling amyotrophic lateral sclerosis has followed encephalitis, the latent period has been variable but usually long[5] so that cases occurring at any one time might be related to preceding epidemics if they are related to encephalitis at all. Since encephalitis has probably been present on Guam for a long time, such a relationship remains a possibility. However, it is unlikely that Japanese B infection is the cause of amyotrophic lateral sclerosis in the Mariana Islands since the limited geographic distribution of amyotrophic lateral sclerosis does not conform to the much wider distribution of Japanese B infection. Only four of our patients could recall a preceding febrile illness which might have been encephalitis. It remains to be seen whether there is an association of amyotrophic lateral sclerosis, various types of encephalitis, and parkinsonism on Guam.

It does not appear that the combination of symptoms suggestive of both amyotrophic lateral sclerosis and parkinsonism in the patients we saw resembled the syndrome of Jakob which Wilson[6] describes and refers to as "corticostriatospinal degeneration." Such cases, as well as those described by Worster-Drought and associates[7] and by Davison,[8] are said to be of rather short duration, are associated with mental deterioration, and may show sensory dysfunction. Our patients had had their symptoms for several years and did not present signs of mental retardation or sensory dysfunction.

Laboratory studies. Laboratory studies are mainly of value in ruling out other disease entities. Koerner described the findings in 11 of his patients for whom such data were available. Two had positive blood Kahn reactions. However, the spinal fluid Kahn reaction in the two patients was negative, and both were considered to have latent yaws, "a condition which was not uncommonly seen."[2]

Of the 46 patients whom we saw, 16 had blood Kahn reactions reported. Twelve were negative; four were positive. Three of the latter four also had cerebrospinal fluid examinations; in these patients Kahn, cell count, protein, and colloidal gold reactions were normal.

Examination of the hospital records on all patients in the "collective series" of 124 cases on Guam and Rota (this collective series includes those patients seen by us, reported by Arnold and associates, Koerner, or Tillema and Wynberg, or other patients who had died since 1950) showed 35 for whom there was a blood Kahn reaction reported. Of these, 28 were negative and seven were questionable or positive. In five of the latter seven, the spinal fluid Kahn reaction was negative; the other two were not reported. In all patients in whom spinal fluid was examined (35 cases), the spinal fluid Kahn reaction was reported for 28; they were all negative. A specific cell count was re-

ported for 25; in 19 there were five or fewer cells per cu. mm., the other reports read eight, ten, 11, 13, 13 and 24 cells per cu. mm., respectively. Of the patients with the high counts, we personally examined only those with eight and 11 cells. The others were dead and had been included in Arnold's and Koerner's series. The colloidal gold curve was normal in the 12 cases in which it was reported. In 30 cases, the total protein was reported; in 25 of these it was between 20 and 45 mg. per 100 cc., in four it was between 46 and 50 mg. per 100 cc., the remaining value reported was 60 mg. per 100 cc.

Ova and parasites were frequently noted in the stools of patients, but since intestinal parasites are common in the general population no conclusions regarding their significance can be drawn in the absence of carefully controlled studies. Similarly, elevated eosinophil blood counts were also noted frequently in our patient group as well as in patients admitted to the hospital for other reasons.

Pathologic anatomy. Muscle biopsies in three patients with advanced disease were obtained during our visit on Guam. The sites selected were deltoid muscles in which prominent fasciculations but only moderate atrophy or weakness were noted. In addition, we also obtained sections and blocks of central nervous system tissue from two other patients, one of whom had been examined three years previously by Koerner and the other whose disease was diagnosed more recently at the Guam Memorial Hospital.*

Dr. George P. Sayre† studied the microscopic sections of the muscle and nervous system. A summary of his report is presented below.

Muscle and nervous system biopsies. The sections showed groups and discrete bundles of atrophic muscle fibers in proximity to groups of normal-appearing muscle fibers. In the former, the sarcolemmal nuclei were found in clumps and more frequently in rows in a hypolemmal position. Such nuclei were especially prominent about the markedly atrophic fibers where they were dark-staining and irregular in size and shape (figure 2). The skin and subcutaneous tissue which were included in one specimen were normal.

In one specimen there was particularly marked variability in the size of the muscle fibers. Some were enlarged; many were quite small. The larger cells stained normally with good cross-striations; the smaller fibers were associated with an increased number of nuclei and were frequently separated from each other and from surrounding muscle fibers by fat cells. Some muscle fibers of intermediate size stained homogeneously and were infiltrated with sarcolemmal nuclei and a few macrophages.

These findings are compatible with chronic muscular atrophy.

A brief case history and summary of Dr. Sayre's description of nervous system specimens in two patients are presented:

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*Dr. M. Gerundo, pathologist, Guam Memorial Hospital, Agana, Guam, kindly provided the central nervous system specimens.

†Member, section of pathologic anatomy, Mayo Clinic, Rochester, Minnesota.

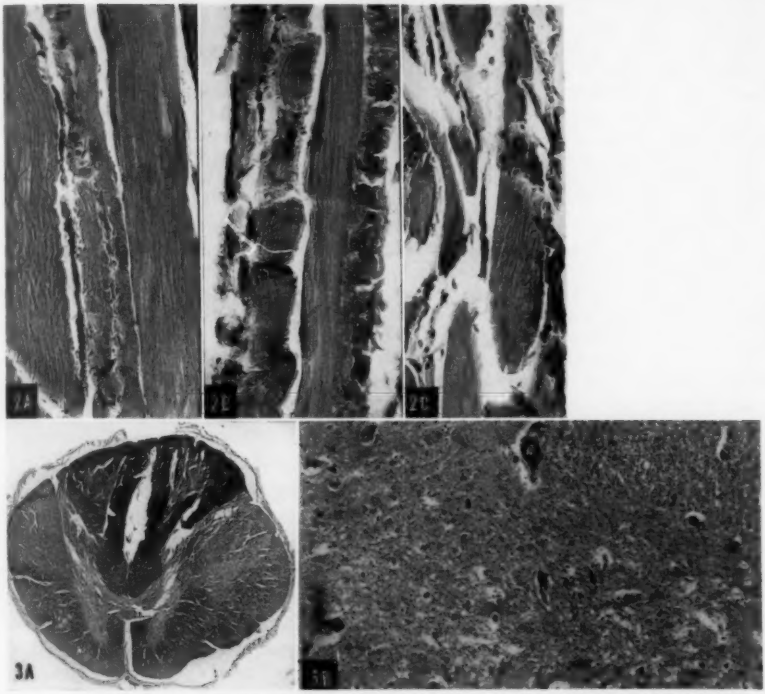


FIG. 2. Biopsy specimens of deltoid muscles of three patients with amyotrophic lateral sclerosis (hematoxylin and eosin stain).

FIG. 3. *A*. Thoracic segment of the spinal cord; demyelinization of the lateral columns (Weil's stain). *B*. Anterior horn of thoracic segment of the spinal cord, showing loss of many anterior horn cells and pyknosis of remainder (hematoxylin and eosin stain).

M.A.A.—Chamorro housewife from Umatac. Her father and two of her six siblings had died of "paralysis." Onset at age 41 years, with weakness and atrophy of small muscles of hands, was first noted in 1947. She was examined in November 1949 by Koerner and it was found that her mental status, sensorium and coordination were normal. She had weakness and atrophy of the intrinsic hand muscles, especially on the left side. The patellar and the upper extremity deep tendon reflexes were moderately hyperactive, and the Hoffmann and Babinski responses were absent. There was slight atrophy of the tongue. Koerner's diagnosis was that of early amyotrophic lateral sclerosis. The patient's condition gradually progressed with the development of spasticity of gait, dysarthria, and dysphagia. She was readmitted to the Guam Memorial Hospital in August 1952, where the diagnosis of advanced amyotrophic lateral sclerosis was made. She died on March 3, 1953.

Sections of the cerebrum and brain stem and multiple sections of the spinal cord were examined. The cortical sections did not include motor cortex. With the exception of two small areas of acute cortical neuronal degeneration and some evidence of edema, the cortex was essentially normal. Sections of the medulla revealed partial demyelinization of the pyramidal tracts. Multiple sections of the spinal cord showed persistent degeneration of the posterolateral columns, including the areas usually designated as corticospinal and cerebrospinal tracts. These latter sections also revealed neuronal degeneration and

loss of cells mainly in the anterior horns. There were some normal-appearing neurons in this area; others, however, showed varying degrees of pyknosis, atrophy, and lipoid deposition. Although it is frequently difficult to ascertain whether the number of anterior horn cells varies from normal, there appeared to be a definite loss of anterior horn cells in these sections beyond that which could be considered due to chance sectioning. This microscopic picture of the specimen is compatible with amyotrophic lateral sclerosis.

J.C.S.N.—Male, village Sinajana. Onset December 1949, age 41 years, with progressive difficulty in speaking. Later, the patient noted progressive weakness and atrophy of muscles of hands and difficulty in moving lower extremities. He had progressive dysarthria and dysphagia with nasal regurgitation and died on May 11, 1953. Family history was negative for "paralysis." Clinical diagnosis: Amyotrophic lateral sclerosis.

Sections of the cerebral cortex were essentially normal; no motor cortex could be identified. Sections of the medulla and spinal cord showed degeneration in areas occupied by pyramidal tracts with demyelinization extending to the posterolateral surface of the cord. In the areas of demyelinization there were swollen astrocytes with hyalinized cytoplasm; the blood vessels were somewhat thickened, occasionally surrounded by lymphocytes, and nearly all were surrounded by gitter cells. The anterior horn cells were somewhat pyknotic and were decreased in number. This microscopic picture is compatible with amyotrophic lateral sclerosis (figure 3).

GEOGRAPHIC DISTRIBUTION AND POPULATION SELECTIVITY

Regions other than the Mariana and Caroline Islands. No reliable basis for comparison of the frequency of amyotrophic lateral sclerosis in different areas has been available. Arnold and associates and Koerner refer to a few selected case sources which are difficult to evaluate.

Mortality rates and estimates of prevalence ratios were therefore developed for the United States, including the Hawaiian Islands, for Canada, Scotland, England and Wales, and Norway. The prevalence for Rochester, Minnesota, a city with about the same population as the native population of Guam, was also determined. The recent crude mortality rates for the countries named were between 0.7 and 1.1 per 100,000 population. The sex ratio for deaths from amyotrophic lateral sclerosis and progressive muscular atrophy is about 1.7 males to 1.0 females. The prevalence ratio for these countries is estimated as being about four per 100,000 population. Only three cases were found in Rochester, Minnesota, for the period 1948 to 1952, inclusive. The details of estimating the frequency of amyotrophic lateral sclerosis are presented in Appendix 1.

One of us (Mulder) interviewed several physicians in Japan, including members of the department of neurology and neurosurgery at the Imperial University in Tokyo. It was the impression of these physicians that amyotrophic lateral sclerosis is a relatively rare disease in Japan.

On the basis of these data, the reports by Arnold and associates of 53 patients* seen in 18 months and by Koerner of 35 patients† seen during the following year would certainly signify an unusual situation on Guam.

*Includes three cases discovered late in their study which were not included in Arnold and associates' paper.

†Koerner's study followed shortly after Arnold and associates had completed their investigation. Nineteen of Koerner's cases had been seen previously by Arnold. Koerner located 16 cases which had not been included in Arnold's series.

Truk. No cases were noted among the Carolinians in the Truk Archipelago (population 15,000). Spot surveys among the population of Moen Island (population 2,600) revealed no cases; no amyotrophic lateral sclerosis death records were found for the Truk District but death certification was of a poor quality.

To our knowledge, no systematic search for cases had been carried out in other areas of the Western Pacific. Koerner[2] reported that the disease was apparently not prevalent outside of Guam, and Arnold[9] has informed us that medical personnel whom he contacted on Ponape, Karor, and Palau between 1947 and 1949 could recall no cases among the Carolinians on these islands.

Saipan. The population of Saipan in 1953 was 4,300 Chamorros and 1,050 Carolinians. One Chamorro patient with amyotrophic lateral sclerosis was found. Histories of four other Chamorro patients who had died in 1890, 1927, 1929, and 1950 respectively, were obtained by inquiry during the examination of the adult population. On Saipan, two deaths from amyotrophic lateral sclerosis out of a total of 600 detailed death records from 1945 to 1953 were recorded. One of these was a Chamorro female and the other was said to be a Carolinian female who had been born on Guam but had come to Saipan many years before. Although amyotrophic lateral sclerosis is present on Saipan, it would appear to be less prevalent than on Guam or Rota.

Rota. The population of Rota is about 950 Chamorros and a few others of mixed Japanese and Chamorro ancestry. Amyotrophic lateral sclerosis had not been reported on Rota previously. On a brief visit we found four native Rotanese males with the disease. One was classified as certain, two probable, and one possible. One Rotanese female had moved to Guam about the time of onset of her illness one year previously and is included in the Guam cases. Since many of the elders in the population were well acquainted with "lytico," it has apparently been prevalent on Rota for many years. Unfortunately, hospital records and mortality statistics were not available for any period.

TABLE 1
SOURCES OF AMYOTROPHIC LATERAL SCLEROSIS CASE HISTORIES COLLECTED ON GUAM

Source of Case	*Total number*	*Number of new cases**
Arnold and associates (late 1947 to early 1949)	48†	48
Koerner's cases, observed (late 1949 to 1950)	35	16
Koerner's cases, hospital abstracts of patients deceased prior to 1949	16	6
Present study, August, 1953 (includes patients previously seen by Tillema)	42	37
Other sources (patients who had died between 1950 and 1953 who had not previously been included in any survey)	13	13
Total cases in the series		120

*—New cases refer to those patients not reported in the collection of a previous investigator.

†—Fifty-three cases had been included in the study; however, five patients who were still living at the time of our survey were found not to have amyotrophic lateral sclerosis, three had rheumatoid arthritis with muscle atrophy, and two had no neurologic dysfunction.

Guam. The permanent population of Guam is about 29,000. All except 2,000 or 3,000 are Chamorros. The rest are predominantly Caucasian; there are only a few hundred each of Japanese or Chinese ancestry.

We observed 42 Chamorro patients with amyotrophic lateral sclerosis and located clinical reports on 13 others who had been hospitalized and had died since 1950. These cases, when added to those previously reported by Arnold and associates and Koerner, provided a series of 120 cases for statistical analysis. The sources of these cases are shown in table 1.

Only one of these patients was not a Chamorro. He was a full-blooded Japanese who had been born in 1879 and had moved to Guam in 1905 where he married a Guamanian woman. Arnold had first examined the patient in 1948 but had not indicated in his published report that any non-Chamorro on Guam had been afflicted.

Because of the important etiologic implications of even a single non-Chamorro case on Guam, the patient's family was interviewed and his brief hospital record was reexamined. The history we obtained indicated that the patient had been well until he sustained a relatively sudden illness at the age of 69 years which resulted in bulbar palsy and possibly a right hemiplegia. He survived only three months; there was no necropsy. The history is so unlike that of the other cases from the standpoint of onset, duration, and clinical picture that there is some doubt that he should have been included.

There was one other non-Chamorro patient. This was an enlisted Navy man, born in Pennsylvania, who was stationed on Guam from May to December 1950. His earliest symptoms had occurred in February 1950 while he was stationed in San Francisco, prior to his arrival on Guam. He was returned to the United States for discharge. He is not included in our series of cases.

An attempt was made to determine how many U. S. Navy personnel who received a medical discharge for amyotrophic lateral sclerosis had been stationed on Guam. Ten men (nine enlisted and one officer) received a medical discharge for this disease from the U. S. Navy from 1948 to 1952, inclusive. Four of these had been stationed on Guam, one is the Pennsylvanian described in the previous paragraph whose onset of symptoms preceded his arrival on Guam; two others were native Guamanians. Only one (the officer) had been stationed on Guam and other Mariana Islands and then only for a period of four months in 1946.[10] It is not possible to assess residence in the Mariana Islands as a possible causative factor; however, it is clear that many cases occur without any such exposure.

More than 15,000 male laborers from the Philippine Islands have been employed on Guam annually since 1949. Most were less than 35 years of age and remained on Guam for less than two years. They usually returned to the Philippines after successfully completing a term of employment of a year or two. As far as can be determined,[11,12] none of these employees had developed amyotrophic lateral sclerosis on Guam; however, it is unlikely that any of them developing insidious weakness which would prevent their working would remain on Guam for a sufficient period of time for the disease to become

TABLE 2

AMYOTROPHIC LATERAL SCLEROSIS IN THE MUNICIPALITIES OF GUAM, THE VILLAGE OF ROTA, AND THE VILLAGES OF SAIPAN

Municipality or district	*Population August 31, 1952*	*Number of patients living on August 1, 1953*	*Prevalence per 100,000 population on August 1, 1953*	*New cases developed during residence*	*Annual incidence per 100,000 population**
Guam	(U. S. citizens)				
Northern					
Dededo	1,555	0	0	2	20
Yigo	865	5	580	7	120
Central					
Agana	706	1	140	1	20
Agana Heights	1,596	2	130	7	70
Agat	1,970	1	50	3	20
Asan	1,377	0	0	0	0
Barrigada	4,803	2	40	8	30
Mongmong-Toto	1,464	2	140	5	50
Ordot-Chalon Pago	1,178	2	170	4	50
Piti	1,054	1	90	2	30
Santa Rita	1,398	1	70	2	20
Sinajana (includes Agana Vista and Price)	3,901	8	210	14	50
Tamuning-Tumon	1,883	4	210	10	80
Yona	1,466	2	140	6	60
Southern					
Inarajan	1,484	3	200	3	30
Merizo	1,037	1	100	2	30
Talofofo	985	3	300	4	60
Umatac	601	4	670	10	250
Residence unknown				1	
Total	29,323	42	140	91	50
Rota					
Village of Rota (the only village)	950	4	420	4	90
Saipan					
Chamorro villages	4,300	1	20	–	–
Carolinian villages	1,050	0	0	–	–

*–Annual incidence is calculated as an average rate per 100,000 population over the 6-7/12 year period from January 1, 1947 to August 1, 1953, on Guam as follows:

$$\frac{\text{Number of new cases} \times 100{,}000 \text{ pop.}}{\text{Village population} \times 6\text{-}7/12}$$

On Rota, the average rate is determined for the cases in the 4-7/12 year period ending August 1, 1953.

fully manifested. We have not as yet been able to follow up the thousands of Filipino workers who have already returned to the Philippines in order to determine whether amyotrophic lateral sclerosis occurs more frequently among them than among those men who did not go to Guam.

The distribution of living patients by village of residence at the time of our survey is shown in table 2. The prevalence rate in round numbers for each village is also given; although the populations of the villages are small, these rates have been computed for 100,000 population since this is the customary basis for comparisons. The rates are variable and it has not been possible to correlate these findings with any other information on the population we now possess. The places of residence at time of onset of all cases which began after January 1, 1947, on Guam and after January 1, 1949, on Rota are also given in this table. The average annual incidence rates by village are also shown in figure 4.

There are several possible explanations of the apparently erratic distribution.

1. The population of northern and central Guam was uprooted and became redistributed after the war. Prior to the war, about half the population of Guam resided in Agana; when that city was destroyed in 1944, most of the population settled in other communities or established new communities on the island. Tillema and Wynberg[3] attempted to plot the distribution of their cases by place of birth; the highest rate was noted in the southern village of Umatac. The rate diminished in a variable fashion toward the central and northern parts of the island.

2. In some communities, for example Asan, a large portion of the population are not Chamorros but civil service employees from continental United States. The distribution of the Chamorro population alone was not available.

3. The principal source of data on cases in the various surveys proved to be the local public health nurses. Some of the nurses appeared to know the disease and their communities better than other nurses. In smaller and particularly semirural communities, the nurse was usually well acquainted with each family and recorded rates in these communities, except for Agana which is still in an unsettled state, are high. On the other hand, in Umatac and Rota some factor common to the populations there may be responsible for the very high rates. As noted in Appendix 2, the "purest strain" Chamorros probably reside in Umatac and on Rota, and the people of these two villages may have the same ancestry. Additional data for Guam, presented in the section on mortality below, suggest that Umatac has been the community with the highest rates, at least since the early part of the present century.

FREQUENCY OF AMYOTROPHIC LATERAL SCLEROSIS ON GUAM AND ROTA

Measurements of the impact of a disease on the population may take the form of prevalence, incidence, or mortality rates. The term "prevalence," as used here, refers to the number of cases of disease found in a community as of a particular date, without regard to time or place of onset of any case. The term "incidence," on the other hand, refers to the number of cases of disease newly developed in a community in a specific time period, usually a year. Thus, the terms "incidence" and "prevalence" are quite distinct in their implications.

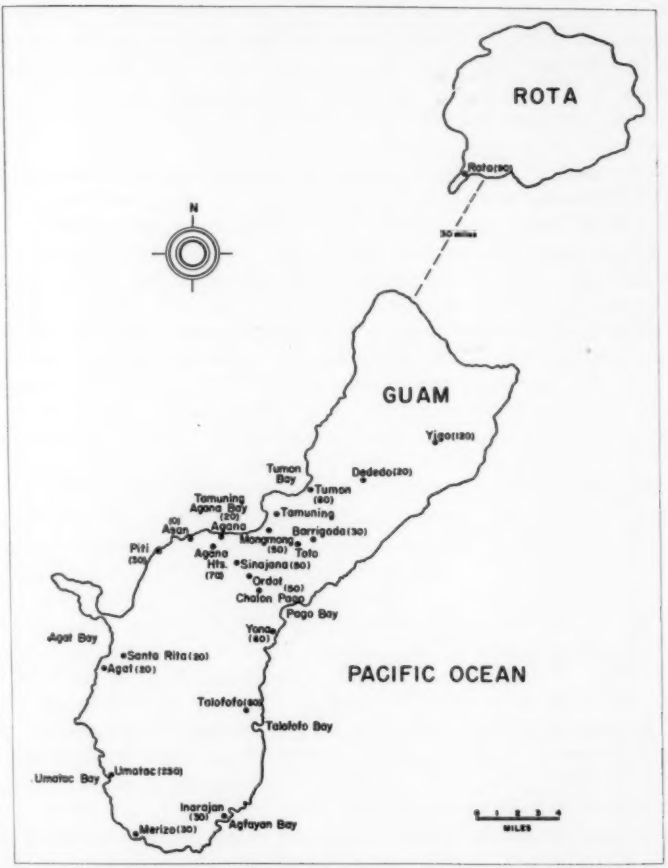


FIG. 4. Map of Guam and Rota, with villages marked, followed by the average annual incidence per 100,000 population in parentheses.

Guam. On August 1, 1953, there were at least 42 patients with amyotrophic lateral sclerosis on Guam; 25 were males and 17 were females. Forty-one were classified as clinically certain or probable, one as possible. One of the 42 was a Rotanese (Chamorro) woman who had arrived on Guam about the time of onset of her symptoms; the remaining 41 were Guamanian Chamorros.

The prevalence rate per 100,000 permanent population, based on these cases, is 174 for males, 114 for females, and 143 for both sexes combined.

At any time between January 1948 and July 1949, no more than 36 of Arnold and associates' 48 patients who were included in the collective series

(table 1) were living. On the basis of the population at that time the prevalence rate per 100,000 would be about 138. However, this does not necessarily mean that the prevalence rate has increased in the last five years, since the difference is not statistically significant, and it is likely that all surveys conducted to date have located only a variable proportion of the total living patients.

On the basis of evidence presented in later paragraphs, it is believed that the present survey was successful in locating only about two thirds to three fourths of all living amyotrophic lateral sclerosis patients on Guam. Some were missed because of obvious deficiencies in the method of study, since a house-to-house survey of the entire island was impractical at this time, and our case-finding sources were limited to those records or persons which were most likely to provide the majority of diagnosed cases. However, there were numerous instances in which diagnosed cases were omitted from the hospital diagnostic files and were located only after we had received information regarding hospitalization from another source of information. A number of death certificates for known patients who had died either could not be found or the death was recorded as due to some other cause; several cases known to us from hospital records were unknown to the local public health nurses.

Many patients with minimal disease were probably missed. It was noted earlier that the average interval between onset and first medical care for our patients was about one year. As pointed out later, the average duration of disease from onset to death is about three years, so that for every two patients in whom the condition has been diagnosed there would probably be one who had early and undiagnosed disease. Thus, this survey probably missed the prediagnosis cases, which amount to about one third of the total cases. Since some cases came to medical attention only at or immediately prior to time of death, it is likely that some patients recognized the disease as one for which there is no treatment and refused to seek any medical aid. The absence of severe pain in this disorder is probably the principal reason why many patients did not seek medical care earlier.

It is believed that the correct number of living patients on Guam at this time is about 60 and that the correct prevalence rate approximates 200 per 100,000 population.

Rota. Four male patients were located in our survey of Rota. Three of the four were born on Rota, the other on Guam. The population of Rota, the only village on the Island of Rota, is 950 Chamorro people. In view of the fact that our survey of Rota was very brief and because there were no satisfactory hospital or mortality records, we must assume that all the frequency values for Rota are incomplete. However, the evidence at hand suggests that amyotrophic lateral sclerosis on Rota is at least as serious a problem as it is on Guam.

INCIDENCE RATES

Guam. The average annual incidence from 1947 to August 1953 is based

TABLE 3
NEW CASES OF AMYOTROPHIC LATERAL SCLEROSIS ON GUAM AND ROTA, JANUARY, 1947, TO AUGUST, 1953

Year of onset of symptoms	Number of new cases	
	Guam	Rota
1947	20	
1948	10	
1949	19	1
1950	11	0
1951	16	0
1952	11	3
January 1 to August 1, 1953	3	0
After January 1, 1947, but date unknown	1	0
Subtotal	91	4
Onset prior to 1947	29	0
Total	120	4

on all cases in the collective series whose onset occurred after January 1, 1947. The distribution of cases by year is shown in table 3. There is a suggestion that the number increases in alternate years, but it is difficult to be sure since the date of onset as given by some patients may not be exact. The average number of new cases per year is about 15. The small number of new cases reported for the first seven months of 1953 is further evidence of the delay in diagnosis following onset of symptoms.

For reasons stated previously, it is likely that several cases have been missed each year; an average incidence of 20 cases per year is probably a more accurate estimate than 15. On this basis the average annual incidence rate

TABLE 4
AMYOTROPHIC LATERAL SCLEROSIS INCIDENCE ON GUAM BY AGE AND SEX

Age at onset, years	Male			Female		
	Cases*	Population (1952)	Rate per 100,000 population per year†	Cases*	Population (1952)	Rate per 100,000 population per year†
0-19	0	8,739	0	0	8,137	0
20-24	2	1,213	24	1	1,304	12
25-34	13	1,575	126	7	1,984	53
35-44	29	1,324	333	12	1,404	129
45-54	25	836	455	15	931	245
55-64	8	505	240	3	572	79
65 and more	2	317	96	1	482	32
Age unknown	2					
Total	81	14,509	85	39	14,814	40
Median age in years	43.8			44.5		
Mean age in years	43.8			44.0		

*—Cases from collective series January 1, 1947 to August 1, 1953.
†—Calculated as an average annual rate for the period January 1, 1947 to August 1, 1953.

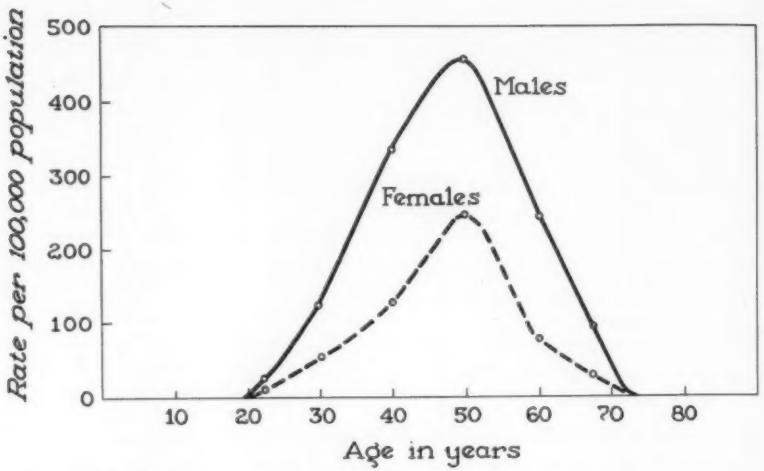


FIG. 5. Amyotrophic lateral sclerosis incidence rate per 100,000 population on Guam, by age and sex. Source: Table 4.

would be about 70 per 100,000 population per year. If the rate is determined for the population age 20 years and more (total in 1952 about 13,000), the average annual incidence rate for the population at risk would be about 150 per 100,000 per year. (For comparison, the highest estimated annual multiple sclerosis rate in the United States or Canada for the corresponding age groups would be about 4 per 100,000 per year).

The age distribution at time of onset for the cases in the collective series is given in table 4 and illustrated in figure 5. For both sexes, the curve rises rapidly above age 20 years and reaches a peak in the 45 to 54 year age group; above this age group the curve drops off even more sharply. For all age groups the incidence rate for males is about twice as high as that for females.

The average age at onset for each sex is about 44 years of age. The youngest was 20 years, the oldest 69 years, in the collective series. In the group of patients we observed personally, the youngest was 20 years and the oldest 60 years of age.

Rota. The age at onset for the four male Rotanese whom we observed was 41, 59, 40, and 52 years, respectively.

MORTALITY AND MORTALITY RATES

Mortality on Guam. (From examination of death certificates). It was our good fortune to find the records of cause of death for the years after the termination of the Spanish occupation of Guam. This valuable source of information was one of the few pre-World War II government records that were not destroyed during the war. There was an occasional diagnosis of progressive muscular atrophy as early as 1904 (Appendix 3). The diagnosis of "amyo-

trophic lateral sclerosis" appeared on a death certificate first in 1931 and reports of this cause greatly increased in relative frequency in later years. Throughout the entire period from 1904 to the present there were many deaths listed as due to "paralysis" (Chamorro translation – "lytico" or "paralytico") in people of middle age. Three such deaths were recorded in 1904 in the first volume of native death records kept by the governor of Guam. The records were still in Spanish and the causes of death as translated are "a paralysis of two years" in a 33 year old male, "a paralysis of one year" in a 50 year old male, and "a paralysis of three years" in a 34 year old male. (All three are from the District of Merizo, which includes the village of Umatac). Until recent years, only about one third of the death certificates had the cause of death reported by a physician; most of the reports were completed by the village lay commissioner and a large proportion of the certificates had no cause of death reported.

TABLE 5
CAUSES OF DEATH REPORTED FOR AMYOTROPHIC LATERAL SCLEROSIS PATIENTS ON GUAM WHO DIED BETWEEN JANUARY 1, 1947, AND AUGUST 1, 1953

Cause of death reported	*Number*	*Per cent of total*
Amyotrophic lateral sclerosis	28	39.4
Paralysis	21	29.6
Progressive muscular atrophy	1	1.4
Other causes (not neurologic)	9	12.7
No death certificate found	12	16.9
Total	71	100.0

For the period 1947 to the present study, it was possible to determine the reported cause of death for many patients who were known to have amyotrophic lateral sclerosis. Table 5 shows that for almost one third of these the term "paralysis" was still being used. It is also of interest that for 13 per cent of the patients the immediate cause of death such as inanition or pneumonia rather than amyotrophic lateral sclerosis was given, and for 17 per cent of the patients who were known to have died there was no death certificate.

In addition to the 21 deaths from "paralysis" for which we had clinical data to verify the diagnosis of amyotrophic lateral sclerosis, there were eight other deaths reported after 1947 as due to amyotrophic lateral sclerosis and eight due to paralysis which we were unable to trace. In every "paralysis" death after 1947 for which we were able to obtain clinical data, there was evidence that amyotrophic lateral sclerosis was the cause of death. We have thus assumed that the large majority of the paralysis deaths after 1904 are due to amyotrophic lateral sclerosis. Further support for this assumption is found in comparing the mean and the median ages at death for amyotrophic lateral sclerosis and paralysis.

There were 40 deaths reported as amyotrophic lateral sclerosis from 1931 to 1953; the mean age at death was 47.4 years and the median was 47.3 years.

TABLE 6

DEATH RATIO AND DEATH RATES PER 100,000 "SUSPECT AMYOTROPHIC LATERAL SCLEROSIS" ON GUAM FOR PERIOD 1902 TO 1952, INCLUSIVE

Year	Suspect ALS*	Average number per year	Approximate population	Total deaths	Death ratio ALS/total deaths	ALS deaths per 100,000 population per year for designated period	Average age, years
1902-1906	13	2.6	10,000	1,131	11:1,000		
1907-1911	5	1.0	11,600	1,445	4:1,000	18	49
1912-1916	6	1.2	13,000	1,474	4:1,000		
1917-1921 (Influenza pandemic)	1	0.2	13,700	2,030	0.5:1,000	6	50
1922-1926	3	0.6	15,200	2,021	1:1,000		
1927-1931	5	1.0	17,400	1,918	3:1,000	5	46
1932-1936	4	0.8	19,500	2,263	2:1,000		
1937-1941	7	1.4	21,500	2,280	3:1,000	6	47
1942 (Japanese occupation)							
1947-1951	43	8.6	27,100	1,464	30:1,000	32	46
1952-1953	12	12.0	30,500	291	41:1,000	39	56

*—ALS=amyotrophic lateral sclerosis.

From 1904 to 1953 there were 75 "paralysis" deaths; the mean age at death was 50.2 years and the median was 48.9 years. Eighty per cent of the paralysis deaths occurred between the ages of 27 and 60 years, 15 per cent between the ages of 60 and 70 years, and five per cent over the age of 70 years. Most of these latter deaths were probably due to cerebral vascular disease.

Table 6 is based on the amyotrophic lateral sclerosis, paralysis, and progressive muscular atrophy death records from 1902 to 1953. The average annual death ratios and annual death rates fluctuate widely with time; this might suggest a variation in the biologic factors responsible for the amyotrophic lateral sclerosis in the population. However, our examination of the death certificates revealed the following reasons for such a fluctuation:

1. The quality of reporting is variable. Prior to 1941, the policy of the U. S. Navy resulted in frequent changes in the medical personnel assigned to treat the civilian population. At times almost all records were signed by village commissioners or pharmacist mates; at other times, physicians signed a large portion of the certificates but the reported causes were often vague.

2. In the early period and occasionally in more recent years, large numbers of deaths in children due to infectious diseases were reported; there were also many cases in which the cause of death was omitted. These reports have had the effect of lowering the ratio of amyotrophic lateral sclerosis deaths to deaths from all causes. In the postwar years, infant and childhood death rates dropped considerably and although tuberculosis continues to take a high toll in childhood and early adulthood, relatively more people are living into middle age when they are at risk of dying from amyotrophic lateral sclerosis.

TABLE 7
SUSPECT AMYOTROPHIC LATERAL SCLEROSIS DEATHS BY SEX FOR VILLAGES AND DISTRICTS OF GUAM, 1904-1942

Village or district	*Permanent population, 1901 census*	*Number of suspect ALS* deaths*			*"Rate" per 1,000 population†*
		Male	*Female*	*Total*	
Northern and Central					
Agana and its dependent villages (includes Agat)	8,371	31	7	38	4.5
Southern					
Merizo district					
Merizo village	516	2	2	4	7.8
Umatac village	249	6	2	8	32.1
Inarajan district	540	1	0	1	1.9
Total	9,676	40	11	51	5.3

*–ALS=amyotrophic lateral sclerosis.
†–Total number of deaths for entire period divided by total village or district population.

In more recent years, it will be noted that approximately one in 30 reported deaths is due to this cause. Although the amyotrophic lateral sclerosis death rate appears to increase considerably after 1947 in relation to the rates from 1904 to 1942, it was apparent as we examined the records over the years that better reporting as well as the change in the population age distribution due to lower childhood mortality rates were largely responsible for the increase.

It is our impression that amyotrophic lateral sclerosis has been responsible for an unusually large number of deaths on Guam, at least as early as the beginning of the present century. This is supported by family histories in which the description of the cause of death in parents of patients 20 to 30 years before fits that of amyotrophic lateral sclerosis. Amyotrophic lateral sclerosis is not a new disease on Guam.

Because of the redistribution of the population which followed World War II, the suspect amyotrophic lateral sclerosis death certificates up to 1942 were studied to see if there had been any focalization of cases on Guam in the past. Table 7 reveals that the highest rates are found in the more remote Merizo District, and particularly in the village of Umatac. It is likely that under-reporting of deaths increased with the distance from the capital and the hospital in Agana, so that the higher rates in Umatac probably signify a real difference. Although Guam is small, it is probable that village populations in the last century and the early part of the present century were relatively stable. Assuming that the cause of amyotrophic lateral sclerosis on Guam originated in Umatac, the migration of the population around the island in recent generations might account for the irregular spread throughout the island (see table 2).

It is of interest that the ratio of males to females among the deaths in table 7 shows a preponderance of males of over three to one. It is unlikely that the present ratio of about two to one indicates a real change in the sex ratio in

recent years, since it is probable that under-reporting of all female deaths in the past was greater than under-reporting of male deaths.

From 1947 to August 1, 1953, 71 of the patients in the collective series died. In addition, during this period there were eight deaths certified as due to amyotrophic lateral sclerosis and eight due to "paralysis" for which no clinical reports could be located. If these latter are accepted as cases, then 87 persons have died of amyotrophic lateral sclerosis on Guam in a 79-month period. This averages just over 13 deaths per year. Other reasons described earlier probably account for numerous omissions in the death recording even for recent years. Amyotrophic lateral sclerosis is said to be fatal in almost all cases, and it is therefore likely that between 15 and 20 such deaths occur on Guam each year. On the basis of only 15 deaths per year a death rate of 51 per 100,000, or about 65 times that reported in the United States, is obtained.

In the postwar years the number of deaths from all causes on Guam has been 250 to 300 per year. About two thirds of these deaths occur in persons aged 20 to 65 years, the age particularly at risk from amyotrophic lateral sclerosis. In this population, amyotrophic lateral sclerosis is responsible for about eight to ten per cent of all deaths.

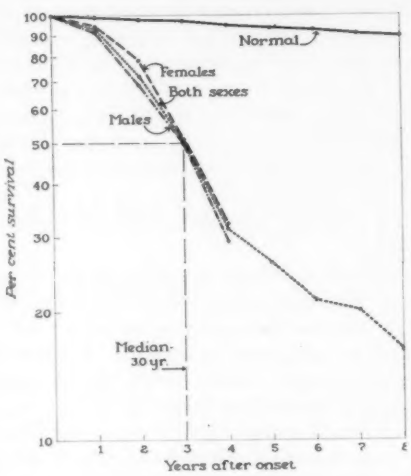
DURATION OF ILLNESS AFTER ONSET

The average duration of amyotrophic lateral sclerosis from onset to death is reported by Friedman and Freedman[13] as about three years. Arnold reported that the average duration was 17 months in the 13 of his 53 Guamanian patients who died during the period of study. Koerner reported the average duration of the seven who succumbed during his period of observation as 22 months.

The fallacy of computing duration of illness in those patients dying during a limited period of study has already been referred to by one of us (Kurland) in another paper[14] as follows: "This method of measuring duration is obviously unsatisfactory for it is bound to give estimates which are too low. Patients in such series who are still living at the end of the study period have on an average a more benign course of the disease than those who died. Exclusion of the living patients results in a selection of patients with higher mortality. Another source of error, also tending to reduce the estimate of life expectancy, is general to all methods that do not involve the follow-up of a number of cases from their onset until death. Because the early symptoms are often vague with an insidious onset, there might be a tendency on the part of the patient to forget such events and to emphasize the (more recent) symptoms."

As we were not on Guam long enough to follow any series of our own cases for the calculation of survival rates, the entire collective series in table 1 were followed. The survival rates for these cases have been determined by the actuarial method described by Berkson and Gage.[15]

Table 8 presents the computations including the per cent of patients sur-



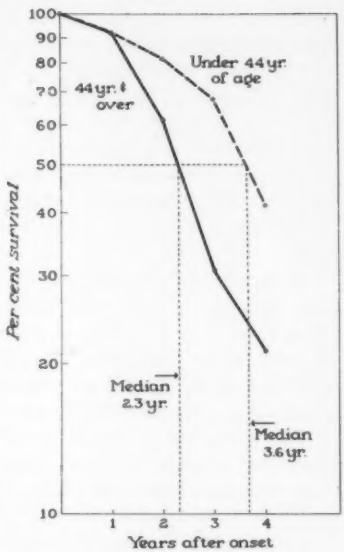


FIG. 6. Comparison of the normal survival curve and the survival curve for male, female, and all amyotrophic lateral sclerosis patients on Guam.
FIG. 7. Comparison of the survival curves of amyotrophic lateral sclerosis patients on Guam whose onset of symptoms occurred prior to and after age 44 years.

TABLE 8

CALCULATION OF SURVIVAL RATES BY THE ACTUARIAL METHOD FOR GUAMANIANS WITH AMYOTROPHIC LATERAL SCLEROSIS*

1	2	3	4	5	6	7
Interval following onset of symptoms	*Last report*		*Total persons living at beginning of interval*	*Persons-adjusted*	*Probability of dying in interval q*	*Survival rate, per cent l*
	Dead	*Living*				
Years 0-1	8	13	118	111.5	0.0717	100.0
1-2	21	10	97	92.0	0.2283	92.8
2-3	18	11	66	60.5	0.2975	71.6
3-4	12	5	37	34.5	0.3478	50.3
4-5	3	4	20	18.0	0.1667	32.8
5-6	2	1	13	12.5	0.1600	27.3
6-7	1	1	10	9.5	0.1053	22.9
7-8	1	2	8	7.0	0.1429	20.5
8-9	4	0	5	5.0	0.8000	17.6
9-10	0	1	1	0.5		3.5

*—For source of cases see table 1. Two cases omitted where date of onset was unknown.

viving for each year after onset of illness. Figure 6 presents a comparison of the survival rates for all amyotrophic lateral sclerosis cases on Guam and also for the two sexes separately; the latter rates were computed for the 79 males and 39 females. The survival curves for the two sexes are practically identical. The curves for the amyotrophic lateral sclerosis patients are compared with a survival curve representing a group of the same mean age as the patient group.* It is obviously considerably lower for each year after the first year than that of the normal population.

The median period of survival for each sex, all ages combined, is three years.

In an attempt to determine the extent to which age at onset influenced the survival rates, the rates were computed for the 59 patients of both sexes whose age at onset was less than 44 years of age and the same number which were 44 years of age and more. The values are presented in figure 7. It appears from this figure that those patients whose onset occurs under age 44 years have a longer duration of life after onset of illness than those age 44 and over.

The mean age at onset for the under 44 group was 35 years; the older group had a mean age of 51 years. Adjustment of the survival rate at three years for those deaths due to causes other than amyotrophic lateral sclerosis might be carried out as follows:

For a population age 35 years, 97 per cent are surviving three years later; for a population age 51 years, 94 per cent are surviving three years later. The adjusted rate for the younger group is 67.7/.97 or 69.9 per cent while that for the older group is 31.4/.94 or 33.4 per cent. However, this is not a precise correction since the older group contains a few persons of age 60 years and over whose chance of survival for three years is very much lower than 94 per cent. However, in the present study the unadjusted rates would seem to illustrate satisfactorily the point that older patients with amyotrophic lateral sclerosis have a poorer survival rate than those whose disease occurs at a younger age.

*Because of the present state of public health on Guam, the group selected was from the Life Table for White Males in the original registration States of the United States, 1909 to 1911. The "normal" survival rates computed are for males aged 44 years.

This paper will be concluded in the next issue of Neurology – June 1954.

TREATMENT REVIEW

This section is designed to give prompt publication to the results of reliable studies in therapy, to record newer methods of treatment, and to encourage research in therapy of neurologic disorders.

AUGUSTUS S. ROSE, M.D., *Section Editor*

POLIOMYELITIS

XI. Treatment

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AS A RESULT of some of the more recent studies in poliomyelitis, it has become apparent that in many cases the entire nervous system is involved, resulting in dysfunction of many body organs. To offer the victims of this disease the full benefits of adequate therapy, the physician not only must consider the degree and severity of the resulting motor weakness but must also keep in mind all possible secondary somatic disturbances and treat or prevent such disturbances in the process of handling his patient properly.

Because of the many new observations that have been made within the past few years, it was felt that a review of the many complications which arise in the course of this disease might be of value, particularly if supplemented by therapeutic suggestions. Since these complications vary with the different parts of the nervous system involved, it was felt best to discuss them in sequence, progressing from the spinal cord to the cerebral hemispheres.

SPINAL POLIOMYELITIS

This is by far the most frequent type of poliomyelitis and, in the absence of cervical cord involvement, does not produce respiratory difficulties or death of the patient. However, in severe cases immobilization of the patient can result in a number of disturbances that must be anticipated and prevented if possible: 1) cardiac involvement; 2) thrombophlebitis; 3) renal calculi; and 4) pneumonia, pulmonary edema, or atelectasis.

Cardiac involvement. As early as 1910 Robertson and Chesley[1] called attention to myocardial involvement in poliomyelitis. Ludden and Edwards[2] studied the heart in 35 fatal cases and found myocarditis in 40 per cent. There was a slight dilatation of the heart in 24 cases. The myocardial lesions varied from mild swelling and fragmentation of an occasional fiber to focal necrosis with actual rupture of the heart wall. Electrocardiographic studies of 265 patients with

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acute poliomyelitis revealed abnormal records in 37 per cent. These abnormalities were more frequent in patients over ten years of age. In cases of spinal involvement alone abnormal tracings appeared in 25.5 per cent, while in bulbar poliomyelitis abnormalities occurred in more than 50 per cent.

Cardiac involvement apparently is frequent enough so that it must be kept in mind in all cases of poliomyelitis. When such a disturbance does appear, it can definitely influence the handling of the patient, particularly with regard to activity. Generally no specific therapy is indicated but caution should be used to prevent too rapid activation of the patient.

Thrombophlebitis. Any patient who is immobilized for any period of time, as are patients with severe spinal poliomyelitis, may develop a thrombophlebitis. Many factors in addition to the prolonged bed rest enter into the development of such a process. Venous stasis may be accentuated by external pressure such as is produced by the respirator. Local injury of the vessel endothelium resulting from too vigorous stretching of a limb or contusion of the veins as a result of too enthusiastic physical therapy may contribute.

The symptoms of thrombophlebitis may be mild or severe. Pain in the involved limb is one of the most constant complaints. It may be mild and well localized, or it may implicate the entire extremity and be throbbing in nature. Often the thrombosed vessel can be palpated. There may be local tenderness in the calf with pain on forced flexion. Gentle but forceful dorsiflexion of the foot with the leg extended will cause severe pain (dorsiflexion sign). The involved limb may become edematous with mottled cyanosis.

The most frequent complication of thrombophlebitis is pulmonary embolism. Large emboli from the femoral, iliac, or pelvic veins produce fatal pulmonary embolism. Smaller emboli produce pulmonary infarcts or pulmonary abscesses, manifesting themselves as sudden chest pain associated with uncomfortable breathing and less commonly, blood-tinged sputum.

Prophylaxis is by far the procedure of choice. Paralyzed patients should be turned frequently and the limbs flexed and extended moderately early in the illness. Excessive dehydration should be avoided. Once the thrombus has formed, every attempt should be made to prevent pulmonary embolism. Active or passive motion of the limb should be avoided and the extremity elevated moderately to avoid edema. Local heat may be applied by use of a cradle. Anticoagulants are very helpful. Dicumerol is the drug of choice since it can be given over a long period of time in doses that keep the prothrombin time at about 2.5 to 3 times normal.

In any large outbreak of poliomyelitis a number of patients needlessly die of pulmonary embolism. This mortality can be reduced by more careful attention to the causative thrombophlebitis.

Renal calculi. Diseases such as poliomyelitis which result in prolonged immobilization in a prone position are frequently complicated by urinary lithiasis. This urinary tract complication is of utmost importance since it may result in decreased kidney function and death from uremia in a patient who, from the point of view of the poliomyelitis, may be showing a very favorable course. Factors which may lead to stone formation include: 1) hypercalcemia from disuse osteoporosis; 2) stasis in the dependent renal calices; 3) overconcentration of urine from dehydration; 4) alkalization of the urine (diet, medication, injections with urea-splitting bacteria); 5) vitamin A deficiency; and 6) foreign bodies in the urinary tract (catheters). Generally the first two factors are the

most important ones.[3]

It is imperative in all such patients to exercise great care in preventing the development of lithiasis. Such procedures must be instituted as soon as the patient becomes immobilized. Once the formation of lithiasis has begun, treatment procedures are of little value.

Osteoporosis and the consequent hypercalcemia may be minimized by the use of active and passive exercise and by frequent and early moving and turning of the patient. Stasis in dependent calices may be counteracted by allowing the patient to spend definite periods in the upright position even if it is necessary to support the patient elaborately. Concentration of the urine can be prevented by supplying a fluid intake that will insure an output of 2,000 cc. daily. The reaction of the urine can be controlled by using an acid-ash diet (avoidance of citrus fruits and leafy vegetables). Absorption of large amounts of calcium can be avoided by reducing the use of acids or acid salts and by avoiding large amounts of vitamin D (no milk). Vitamin A is usually given in daily quantities of 10,000 I.U.

Infection of the urinary tract must be prevented and must be watched for by weekly cultures. Effort should be made to keep all catheters, glassware, and tubing carefully cleansed of all traces of salts and sterilized effectively. Antibiotics in small doses are prescribed routinely whenever an inlying catheter is used. Basic aluminum carbonate jel (Basaljel, 30 cc. four times daily) is often helpful in that it minimizes the excretion of phosphorus in the urine and thus reduces the urinary concentration of one of the most important constituents of the stones.

Infections of the upper respiratory tract. These can be very serious disturbances. Toxicity resulting from such infections may further injure anterior horn cells that have already been damaged by the disease, thus increasing the degree and permanence of limb paralysis. Respiratory infections may also increase metabolism and thus heighten the respiratory demand. Hence these respiratory complications must always be anticipated and prophylactic and therapeutic procedures considered.

Everyone coming in contact with the patient during the acute illness should wear a mask to protect the patient from exposure to an upper respiratory infection. All persons with suspected respiratory infections should be kept away from the patient. Antibiotics and other forms of chemotherapy should be used both prophylactically and therapeutically. Generally prophylactic treatment with penicillin is most effective against the organisms most likely to cause pneumonia. Procaine penicillin may be used in doses of 250,000 units twice daily. Finally, patients should be moved frequently, with routine turning at least every hour to prevent hypostasis.

Since atelectasis occurs only if there is difficulty in coughing or inadequate ventilation, it does not have to be considered in this type of poliomyelitis.

Impaired muscles of respiration. The diaphragm and intercostal muscles are innervated by the motor neurons of the upper thoracic and cervical cord. They cause a rhythmic enlargement of the thoracic cage. Effective ventilation is determined by the magnitude of tidal volume; hence slow deep breathing is far more effective in ventilating the alveoli than rapid shallow breathing. In poliomyelitis there is frequently a partial or even complete involvement of the muscles of respiration, and it is extremely important that the physician be alert to detect or anticipate its occurrence early. In some patients complete paralysis may occur so rapidly that corrective measures using the respirator are not immediately available, thus resulting in a fatal outcome. Much more important is the partial or

mild involvement of these respiratory muscles which can be overcome by more rapid but shallower respirations with a consequent smaller alveolar exchange. This underventilation may result in a mild hypoxia in the absence of cyanosis and may be overlooked unless checked for specifically.

A number of clinical symptoms and signs suggest an impending or actual inadequacy of the muscles of respiration and should be checked for constantly in every case of poliomyelitis:

1. Paralysis of the deltoid or biceps muscles, both of which are supplied by neurons situated very close to the cells innervating the diaphragm.
2. Rapid shallow respiration with a flaring of the alae nasae.
3. Purely diaphragmatic breathing or the use of the accessory muscles of respiration.
4. Assymetry of movement of the thorax particularly on deep inspiration.
5. Inability of the patient to repeat three or four numbers without pausing for breath.
6. Protrusion of the epigastrium on deep inspiration when the thoracic cage is splinted.
7. Absence of the normal successive retraction of the lower intercostal spaces (Letten's sign) during inspiration.
8. Inability to sniff (a function carried out by use of the diaphragm).
9. Inability to hold the breath for 15 seconds. Normally a child can hold his breath for 15 to 18 seconds.

When definite loss of respiratory muscle function has occurred, some form of mechanical respiratory aid is necessary. These consist of the tank respirator, the cuirass respirator, or the rocking bed. Of these, the tank respirator is by far the most efficient and generally is used during the acute illness. Patients with respiratory difficulty are often tense and apprehensive; hence the physician should prepare the patient for the respirator and should remain with the patient for some time after he has been placed in it. Frequently the patient has difficulty adjusting to breathing with the respirator. A little help and guidance from the physician may go a long way in alleviating this problem. As soon as the patient is placed in the respirator, its rate and pressure must be adjusted to the needs of the patient. In general, alterations in depth are much more beneficial than alterations in rate. Under proper regulation, all signs of hypoxia such as apprehension, restlessness, pallor, anxious facial expression, and cyanosis should disappear and the patient's breathing should synchronize with that of the respirator. Generally in children the rate varies between 24 to 30 and the depth from −12 to −5; in adults the rate varies from 18 to 20 and the depth from −15 to −18. It must be kept in mind that the gauge on the respirator is often inaccurate and should be checked regularly against a water monometer.

Once the patient is placed in a respirator, there are a number of precautions to be observed.

1. The patient must be kept comfortable within the tank by constant attention to the intertank temperature, proper care of the skin, adequate movement of the limbs, and attention to bowel and bladder function. Fever and the heat within the tank may result in excess fluid loss which must be replaced either orally or by vein if swallowing is impaired. In many cases urinary retention occurs during the early phase of the illness necessitating an indwelling catheter. In such cases Gantrisin should be administered to prevent bladder infection. The availability of a dome attachment to the respirator by means of which positive pressure can be given for short periods of time greatly facilitates the care of the limbs, skin, and sphincters. If no dome attachment is available, then one can request the anesthesiologist to

"bag breathe" the patient for short periods while routine body and limb care are being carried out. "Bag breathing" can also be used whenever it is necessary to open the respirator for emergency procedures such as beginning intravenous therapy, cutting down on a vein, performing a tracheotomy, and even giving the patient an enema.

2. Pulmonary edema and pulmonary atelectasis must be prevented. These complications are not common in pure spinal poliomyelitis but usually occur when there is associated bulbar involvement.[4,5] They will be discussed in detail under bulbar poliomyelitis.

3. The patient should be transferred to a cuirass or chest respirator as soon as possible. Generally these are not effective in severe acute respiratory paralysis. Their best application is in the convalescent patient who no longer requires the tank respirator but still needs some respiratory assistance. There are two types of cuirass respirators, namely the Monaghan and the Kifa. Often the convalescent patient may progress directly from the cabinet type respirator to the rocking bed. Transfer to either the cuirass respirator or the rocking bed is very important, since it facilitates the care of the patient and enables more intensive physical therapy. For this reason patients should be advanced to these latter forms of respiratory aids just as quickly as possible.

BULBAR POLIOMYELITIS

Most deaths in poliomyelitis can be related to involvement of the brain stem and immediately contiguous brain centers. If the patient is to survive such an involvement, it is imperative that the physician be aware of all possible complications and learn to recognize those symptoms and signs that indicate the nature of the disease process.[6] Only by early recognition and intensive therapy can the mortality rate be reduced in this form of the illness. Basically there are eight types of involvements that must be considered: 1) interference with the airway; 2) impaired respiratory rhythm; 3) vasomotor disturbances; 4) trismus; 5) hypoxia; 6) pulmonary edema; 7) disturbances in acid-base balance; and 8) vomiting.

Obstruction of the airway. This complication results from involvement of the lower cranial nerves, resulting in weakness of the soft palate, the pharynx, and the vocal cords. Initially there is difficulty in swallowing, accumulation of secretions in the oropharynx, and/or hoarseness or a nasal twang to the voice. Examination will reveal pooling of saliva in the throat, nasal speech, laryngeal stridor, and perhaps a weak tongue. When the lower cranial nerves are involved there are many reasons why the airway becomes obstructed and each must be investigated and corrected. Airway obstruction may result from: 1) pooling of secretions due to paretic throat muscles; 2) paralysis of the tongue; 3) reflex spasm of the laryngeal muscles; 4) abductor paralysis of the vocal cords with fixation in the midline; 5) accumulation of secretions due to inability to cough; 6) aspiration of vomitus. The persistence of symptoms of hypoxia, which are discussed later, indicates that the obstruction has not been relieved and that further measures are indicated.

1. Difficulty in swallowing: This complication is fairly easily recognized. Early there is an unusual amount of drooling and the patient constantly attempts to clear the throat. Secretions begin to pool in the throat, the palate becomes paralyzed, and the voice becomes nasal in character. If untreated, the patient begins to show evidence of hypoxia.

In these cases it is imperative that the airway be kept open. This should be attempted at first by postural drainage and mechanical suction. For postural drainage the bed is tilted at an angle of 10

to 15 degrees; the patient generally is more comfortable when lying on the side. Mechanical suction is carried out by means of an electrically-driven suction machine set at 5 to 10 cm. of water. Mechanical aspiration is generally carried out by a catheter passed through the nose and inserted deep into the bronchi. Failure to obtain adequate aspiration or any obstruction to the catheter warrants immediate investigation. If all other methods fail to keep the airway open, one may have to resort to tracheotomy. Tracheotomy avoids any obstruction caused by pharyngeal secretions and prevents acute obstruction from abductor paralysis of the vocal cords. It also has the advantage of enabling the removal of any fluid that might be aspirated. If a tracheotomy becomes necessary there are a number of precautions that must be observed: 1) the stomach should be aspirated prior to surgery to avoid aspiration of its contents; 2) intensive suction will be necessary for hours following tracheotomy; 3) the tracheotomy should be done high in the neck to allow for better care of the patient; 4) the tracheotomy tube must be large, generally a six to eight tube. It must be kept in mind that the air flow through the tracheotomy tube increases by the radius of the tube to the fourth power (air flow = r^4) so that there is a tremendous increase in air flow when larger tubes are used.

After tracheotomy the patient still requires constant care and supervision. It is necessary to continue to aspirate secretions from the pharynx particularly during the first few days after tracheotomy. The tracheal cannula must be inspected and cleared frequently. Often the administration of 50 per cent oxygen through the tracheotomy tube will prove beneficial. In spite of tracheotomy it is advisable to rotate the patient constantly in order to avoid pulmonary hypostasis. This procedure is most satisfactory if the patient is rotated at least 60 degrees or more every hour. If the patient is not in a respirator, the rotation should be more complete, extending to the maximum of 90 degrees. Such a procedure may keep the lungs clear in many patients in whom pulmonary edema is already developing.

There is considerable difference of opinion concerning the indications for tracheotomy in bulbar poliomyelitis. The following criteria have proved most useful in our experience: 1) involvement of the lower cranial nerves with dysphagia occurring early in the disease; 2) appearance of dysphagia with pooling of secretions in a rapidly progressing illness; 3) any case in which the airway cannot be kept open by postural drainage or mechanical suction; 4) an obstructed airway due to reflex spasm of the laryngeal muscles or abductor paralysis of the vocal cords; 5) any patient with pharyngeal secretions who is placed in a respirator; 6) any patient with lower cranial nerve involvement who cannot be watched carefully.

2. Aspiration of secretions or food: This complication produces signs and symptoms of atelectasis with changes in respiration and respiratory sounds, inadequate ventilation, impaired excursion of the chest, and respiratory stridor. It is a very serious complication that requires intensive therapy. The obstructing material must be removed by mechanical suction or by bronchoscopy. Bronchoscopy can easily be carried out through a tracheotomy tube. Vigorous antibiotic therapy should be used to prevent pneumonia or abscess formation.

3. Abductor paralysis of the vocal cords: This complication occurs most acutely in a patient who apparently is getting along nicely; if not recognized it may jeopardize the life of the patient. A severe rapidly developing hypoxia occurs with sudden cyanoses and loss of consciousness. It may be accompanied

by respiratory stridor, aphonia, and dyspnea. This condition requires emergency treatment by immediate intubation or tracheotomy.

Impaired respiratory regulation. Respiration in man is regulated by the small reticular cells situated in the ventrolateral reticular area of the lower medulla.[6] These centers control the rate, depth, and rhythm of breathing and are very sensitive to changes in the carbon dioxide level. Injury to these central respiratory centers interferes with the regulation of respiration and results in inadequate ventilation, insufficient oxygen uptake, and a carbon dioxide retention. Generally an increase in carbon dioxide stimulates the respiratory centers to increase ventilation. In the presence of a damaged center such response is impossible and respiratory acidosis continues to increase with the associated inadequate oxygen uptake. Severe involvement of the respiratory centers occurs in about 25 per cent of all cases of bulbar poliomyelitis.

Clinically irregularities of the rhythm and depth of respiration develop in spite of an adequate airway and intact muscles of respiration. The respirations tend to be shallow and there are often prolonged intervals between respirations. At this point the patient shows some degree of anxiety, restlessness, and increased pulse rate. As failure of the respiratory center progresses, there are increasing periods of apnea with beginning Cheyne-Stokes respiration. The temperature and pulse rate tend upward and the blood pressure may drop to shock levels. The periods of apnea become more prolonged until respirations finally cease.

Since these patients have lost the ability to regulate respirations properly, some type of mechanical respiration is necessary just as soon as clinical signs of inadequate ventilation become apparent, such as anxiety, restlessness, apprehension, rapid pulse, and an increase in blood pressure. These patients often have great difficulty synchronizing their breathing with the respirator. If this difficulty continues to persist and interferes with ventilation, sedation may be used to further suppress the patient's respirations and enable the respirator to take over breathing almost independently.

In most patients with this type of bulbar involvement a tracheotomy is essential when the patient is placed in the respirator. Because of inadequate oxygen uptake in these individuals, oxygen therapy is advisable and can be administered readily through the tracheotomy tube. The concentration of oxygen should not exceed 60 per cent and is best given under a positive pressure of 2 to 6 cm. of water. Any manipulation, such as frequent prolonged suction, which interferes with oxygenation should be avoided. Suction should be carried out quickly. Moisture should be added to the oxygen mixture in order to prevent the trachea and bronchi from becoming too dry. This can be done by means of humidifiers or by tracheotomy inhalators.[7] The adequacy of the oxygen therapy can be followed by use of the oximeter or by determination of the arterial oxygen.

Impaired vasomotor regulation. The centers for the control of circulation in man are composed of the large reticular cells situated in the ventromedial reticular area[6] of the lower pons and upper medulla. Severe involvement of these centers occurs in approximately 5 per cent of bulbar poliomyelitis patients and constitutes an extremely grave complication. The clinical features are very characteristic. These patients have a dusky red, flushed, florid appearance. The lips are deep cherry red. The pulse is rapid, ranging between 150 and 200. It is often irregular and at times difficult to palpate. The blood pressure drops to very low levels and the pulse pressure

may be as low as 10 mm. Hg. Very early these patients show marked restlessness, anxiety, and apprehension. The course of this illness grows worse rapidly and the mortality is high. The skin soon becomes cold and clammy and has a mottled cyanosis. The temperature begins to rise. Terminally, these patients become confused and finally comatose and the heart beat is inaudible before respirations cease.

The treatment of the circulatory type of bulbar poliomyelitis is very unsatisfactory. It is imperative to maintain adequate ventilation and oxygenation, with particular attention to maintenance of a clear unobstructed airway at all times. Oxygen therapy is used to combat hypoxia and to prevent the addition of hypoxic damage to centers already injured by the virus. Supportive measures in combating shock may be used but seem to be of only temporary benefit. Caffeine sodium benzoate (0.5 gm.) can be administered intravenously and may be repeated intramuscularly as often as every hour if necessary. Ephedrine sulfate 25 mg. in solution subcutaneously, desoxyephedrine sulfate 10 mg., epinephrine 3 mg. of a 1:1000 solution intramuscularly, desoxycorticosterone 5 to 10 mg. intramuscularly, or norepenephrine can all be used in the attempt to combat circulatory failure.

Trismus. Pathologically the pons is involved in practically every case of bulbar poliomyelitis.[8] One of the most dramatic clinical manifestations of such involvement is irritation to the motor nucleus of the fifth cranial nerve, resulting in trismus.[8] This complication appears suddenly, usually at the end of the first week of the illness and persists from five to seven days. At times it is extremely painful. The jaws become locked and eating or even talking becomes impossible. This complication may be an extremely dangerous one since the inability to open the mouth prevents adequate removal of secretions with possible obstruction of the airway. In such cases, immediate tracheotomy is necessary to prevent asphyxiation by secretions. Since eating is also impossible, it is necessary to insert a nasal tube into the stomach for feeding purposes.

Hypoxia. Because hypoxia plays such an important role in the symptomatology of bulbar poliomyelitis, it might be well to review briefly this phase of the illness. In poliomyelitis hypoxia may occur from many causes. These are listed according to the nature and location of the disease process.[9]

1. Ninth to twelfth cranial nerve nuclei involvement:
   - (1) Pooling of secretions due to paretic throat muscles,
   - (2) Paralysis of tongue,
   - (3) Obstructed airway due to reflex spasm of the glottis,
   - (4) Obstructed airway due to abductor paralysis of vocal cords,
   - (5) Accumulation of secretions due to inability to cough,
   - (6) Aspiration of vomitus.
2. Respiratory center involvement:
   - (1) Inefficient, irregular, shallow breathing,
   - (2) Periods of apnea.
3. Circulatory center involvement.
4. Bulbar and cervical cord involvement:
   - (1) Any of the above,
   - (2) Involvement of primary and accessory muscles of respiration.
5. Alterations in the lungs:
   - (1) Pulmonary edema,
   - (2) Atelectasis,
   - (3) Pneumonia.
6. Possible contributing causes:
   - (1) Sedation,
   - (2) Anemia,
   - (3) Air swallowing,
   - (4) Hysteria and/or panic.

Any of these causes may produce a definite group of characteristic symptoms and signs which should alert one to the presence of hypoxia. A thorough check

must be made for all factors which may result in deficient oxygenation of the patient. Although the many symptoms of hypoxia have been discussed, it might be well to review them since they comprise an important part of the clinical picture of poliomyelitis.

1. First stage—restlessness, apprehension, anxiety, sleeplessness.
2. Second stage—florid appearance, increasing pulse rate, blood pressure and respiratory effort, euphoria, and a tendency to speak fewer words in one breath.
3. Third stage—dyspnea, cyanosis, rise in temperature, confusion, marked restlessness, and occasional panic reaction.
4. Fourth stage—cyanosis, circumoral twitching, failure to answer questions, delirium, coma, and terminal shock.

The treatment of these various phases of hypoxia have already been discussed under the various causes of respiratory involvement. If a patient with poliomyelitis has a tracheotomy and then develops evidence of hypoxia, there are a number of things that should be checked immediately in order to determine the source of the difficulty: 1) Check the position of the tracheotomy tube in the patient to be sure that the tube is not positioned in the trachea so as to obstruct the opening. 2) If the patient is receiving oxygen, be sure the tubing has not collected fluid. This tubing must be drained periodically. 3) If the patient is also in a respirator, check the pressure, the portholes, the collar, and the screws about the collar. 4) Check for bronchial obstruction using deep suction as far as the tube will go. Bronchoscopy may be necessary if suction is unsatisfactory. 5) Check for pulmonary edema by observing lung excursion. 6) Check for gastric hemorrhage.

Pulmonary edema. The principal factors regulating interchange of water between the pulmonary capillaries and the tissue fluids are the colloid osmotic pressure (blood proteins) and the capillary blood pressure. The former draws fluid into the blood while the latter tends to force water into the tissue spaces. Normally the blood proteins do not pass through the capillary membranes, hence the colloid osmotic pressure within the pulmonary capillaries remains at about 22 mm. Hg. If hypoxia occurs in poliomyelitis the pulmonary capillaries can be injured, thus allowing the blood colloids to pass into the tissues and resulting in an increase in the tissue osmotic pressure and a subsequent increase of fluids in the lung alveoli which produces pulmonary edema. Any inflammatory process similarly injuring the lung capillaries can result in tissue or pulmonary edema. This type of pulmonary edema is best treated by increasing the blood colloids with transfusions of blood plasma, thus replacing the lost colloids.

Pulmonary edema may also result from left heart failure which raises the capillary blood pressure and forces fluids from the capillaries into the alveoli. This complication can be approached through the use of drugs to strengthen heart action.

It is important in such cases to avoid any procedure that suddenly increases intracapillary pressure such as occurs during rapid administration of intravenous fluids. Such fluids must be given slowly over a 24 hour period.

Acid-base balance. The normal blood pH is 7.4. This value is maintained by a balance between acid and base of the blood regulated in part by carbon dioxide exchange in the lungs. In hyperventilation, as occurs in too rapid excursions in a respirator, carbon dioxide is lost and there is also a drop in the normal bicarbonates of the blood. Normally there results a compensatory depression of respiration and an excretion of bases in the urine, thus restoring the proper acid-base balance. If the patient is in a respirator where such a respiratory depression is impossible, then respiratory alkalosis may continue, resulting in severe neurologic complications or even death. Respiratory alkalosis also

results in an increase of blood sodium and an increase in blood chlorides.

Respiratory acidosis can result from a large number of complications of bulbar poliomyelitis such as: 1) pulmonary edema, atelectasis, or pneumonia; 2) intercostal and diaphragmatic paralysis; and 3) injury to the respiratory center in the medulla. In the first two situations there is a disturbance in the removal of carbon dioxide from the blood due to inadequate pulmonary action. Ordinarily as carbon dioxide accumulates in the blood, it results in a stimulation of the respiratory center with an increase in the respiratory rate. Injury to the respiratory center or the use of a respirator both will interfere with this compensatory mechanism, resulting in an increase of the respiratory acidosis. Under such circumstances the partial carbon dioxide pressure of the blood continues to rise, the blood sodium also decreases, the chlorides decrease, and the urine becomes acid in an attempt to reduce acidity of the blood. The patient rapidly loses consciousness and will die unless the acidosis is relieved.

Because of these rapid fluctuations in the acid-base balance in bulbar poliomyelitis, it is imperative to check the bicarbonate, potassium carbonate, sodium, and chlorides, and the reaction of the urine daily in patients severely ill with bulbar poliomyelitis, particularly if the patient is in a respirator. Adjustments must be made in the rate and depth of the respiratory excursions depending upon the acid-base balance. It is important to attempt to keep the values of the blood sodium and chlorides as normal as possible.

Vomiting. Patients with poliomyelitis may develop vomiting due to many causes. If vomiting persists for 24 hours or more, or if gastric suction is applied for the same period of time, grave complications may result due to a disturbance of the acid-base balance. During vomiting or gastric aspiration there is a loss of fluids as well as electrolytes. A patient can lose nearly eight liters of fluids in 24 hours or almost one-fifth the total body water. In addition, approximately 40 to 50 grams of salt per day may be lost, which is almost half of the total body salts and almost five times the daily intake. The gastric juice contains 145 meq. per liter of chlorides but only 15 meq. of sodium so that the greatest loss will be in the chlorides. As a result of the fluid and electrolyte losses from vomiting a number of body changes occur: 1) the extracellular fluid is reduced; 2) the patient develops a metabolic alkalosis because the sodium formerly bound to the chlorides is free to combine with the carbonate because of the loss of chlorides; 3) the kidney excretes an alkaline urine in an attempt to compensate for the alkalosis.

In every case of vomiting the electrolytes and fluids lost should be measured and replaced. It is possible to replace most of these losses by the administration of saline intravenously or by stomach tube.

POLIOMYELITIS OF HIGHER CENTERS

Hyperthermia. Neurogenic hyperthermia can result from damage to the hypothalamus in poliomyelitis.[10] Apparently it is the anterior hypothalamus that is active in reducing body temperature and when injured will allow for the development of hyperthermia. Since the hypothalamus is frequently and consistently involved in most causes of bulbar poliomyelitis, one can anticipate that a number of patients will have unstable temperature regulating mechanisms and every precaution will have to be observed to prevent or to minimize excessive temperature elevations which may complicate the care of these very ill patients. Hot packs must be avoided in such cases. If the patient is in a respirator every attempt must be made to keep the pa-

tient cool within the respirator by use of ice bags and other cooling devices. Hydration should be adequate.

Once the temperature rises to unusual levels and remains high in spite of subsidence of the acute illness, every means should be employed to reduce the body temperature. Antipyretics may be tried but generally are not very effective. Alcohol sponges, ice packs, and sponges with cold water may be helpful. The limbs should be massaged vigorously to increase peripheral circulation. Colonic irrigation with ice water often will be useful in producing a rapid fall in body temperature. If possible, these patients should be kept in an air-conditioned room until the body temperature becomes stabilized.

Gastric hemorrhage. Because of hypothalamic involvement in poliomyelitis, specific gastrointestinal lesions occur, many of which play an important role in the ultimate outcome and recovery of the patient.[11] During the acute illness, lesions consist primarily of petechiae, ulcerations, and hemorrhage. Early, the patient may complain only of mild abdominal pain or abdominal distention. Many patients refuse food because of the discomfort it produces. At this stage, bleeding is probably mild and no doubt associated with some ulceration. As the bleeding continues, the patient becomes nauseated and vomits small amounts of "coffee ground" material. Generally at this time there is no alteration in the hemoglobin and no evidence of shock. However, the gastrointestinal complaints and sudden appearance of "coffee ground" emesis should suggest the possibility of gastric bleeding and demand adequate investigation for such a complication.

More intense hemorrhage results in marked abdominal distention and the emesis of large amounts of blood which may be "coffee ground" or even bright red. The blood pressure may fall to shock levels and there is a rising pulse rate. In a number of patients, the first indication of such a complication is the sudden appearance of symptoms of shock in a patient who had been doing fairly well. In these patients, the pulse suddenly becomes feeble and rapid, the blood pressure drops, and the skin becomes cold and clammy. Concomitant with onset of the above symptoms, the patient occasionally may lose consciousness or may become confused, apprehensive, or restless.

Gastric hemorrhage in acute bulbar poliomyelitis must be included among the more serious complications of this illness. Severe gastric hemorrhage may be the immediate cause of death and early recognition and treatment of this complication may prevent shock and death. Less severe bleeding, although not responsible for immediate death, may play a role in the unfavorable course of the illness. Certainly tissues already damaged by the infectious process may be even more severely destroyed as a result of decreased nourishment secondary to the loss of blood.

The usual treatment employed for bleeding from a gastric ulcer is followed. The patient is transfused with whole blood, each transfusion consisting of 500 to 600 cc. If the patient is not vomiting, feedings of milk and cream may be instituted fairly promptly, generally as a continuous slow drip through an inlying nasal tube over the 24 hour period. Other antacids may be used, as well as methantheline (Banthine).

Gastric distention. This form of gastrointestinal disturbance is not usually seen in the very acute illness but appears during convalescence.[12] At onset the patient may complain of a loss of appetite and some nausea and vomiting. Generally the vomitus contains only mucus. In the more severe cases, the patient develops severe abdominal distention and often acute abdominal pain. In patients with

limited respiratory reserve, particularly in those who have weak diaphragmatic action, this distention may further limit respirations and produce acute respiratory embarrassment which may result fatally if not recognized and remedied. These deaths are particularly tragic because they are easily prevented simply by aspirating the stomach and thus relieving distention.

Involvement of the cerebral hemispheres. The cerebral hemispheres are involved in about 75 per cent of cases of bulbar poliomyelitis. In most patients, the lesions are localized to the motor cortex, involving primarily the third and fifth cortical layers.[13] In many patients with bulbar poliomyelitis there is an additional hypoxic factor which often results in a more diffuse neuronal damage that implicates all areas of the brain and produces a more diffuse symptomatology. These symptoms include headache, anxiety, restlessness, hyperexcitability, muscular tremors and twitchings, irritability, confusion, hallucinations, lethargy, coma, and convulsions, especially in children. There may be a marked insomnia; many patients remain awake for several days and nights.[14]

When such symptoms appear they should be first considered due to hypoxia, even if there is no cyanosis. Such a state of hypoxia may be produced by an unrecognized partial obstruction of the airway, a failure of central control of respiration or circulation, an inadequate function of the diaphragm or intercostal muscles, an acute pulmonary edema, or an atelectasis. Once the exact causative factor has been discovered, corresponding therapy can be instituted. In most of these patients, cerebral symptoms disappear after measures are taken to insure adequate ventilation and oxygenation of the patient. This can be accomplished by suction, respirator, tracheotomy, and/or additional oxygen therapy, depending upon the cause of the hypoxia. Sedatives are strongly contraindicated because of their effects upon the respiratory centers. Even strong analgesics should be avoided. One must rely upon aspirin and careful nursing to keep these patients comfortable.

Only when cerebral symptomatology persists after adequate ventilation is achieved can one ascribe the cerebral symptoms to an actual involvement by the virus or irreversible damage by the hypoxic process. In either case treatment must be symptomatic, since most of these symptoms will improve as the patient recovers. In these cases attention must be given to adequate nutrition and the prevention of exhaustion due to overactivity.

SUMMARY

1. Spinal poliomyelitis may be complicated by cardiac involvement, thrombophlebitis, renal calculi, and pulmonary disturbances.

2. Thrombophlebitis may be prevented by frequent turning of the patient, moderate movement of the limbs, and adequate hydration. If present, it should be treated by complete immobilization and elevation of the involved limb, local heat to the extremity, and the use of anticoagulants.

3. The three most common causes of urinary calculi are hypercalcemia from disuse osteoporosis, stasis in the dependent renal calices, and urinary tract infections. These may be avoided by frequent moving of the patient, proper hydration, the use of an acid-ash low vitamin D diet supplemented by basic aluminum carbonate jel, and the prevention of urinary tract infections by proper care of the catheters and small doses of antibiotics.

4. Pulmonary infections may delay recovery by increasing metabolism and the toxicity of the patient. They can be avoided by the use of protective masks, antibiotics, and frequent turning and

moving of the patient.

5. When the upper spinal cord is involved, there is impairment of the muscles of respiration necessitating the use of some type of respiratory aid such as the tank respirator, the cuirass respirator, or the rocking bed. In severe cases the tank type respirator is generally used. In such cases constant vigilance is necessary as to the depth and rate of the respirator, the patient's comfort within the respirator, and the avoidance of pulmonary edema and atelectasis due to obstruction of the airway from an associated bulbar involvement. Transfer should be made to the cuirass respirator or rocking bed just as soon as possible to facilitate care of the patient.

6. For patients in a tank respirator, short periods of positive pressure breathing by means of "bag breathing" or by a dome attachment may be used to facilitate care of the limbs, skin, or sphincters or to institute special procedures such as intravenous therapy or an enema.

7. Involvement of the lower cranial nerves results in dysphagia with an obstruction of the airway from a pooling of secretions in the oropharynx, aspiration of vomitus or food, or a reflex spasm of the glottis. The airway must be kept open by postural drainage, mechanical suction, or tracheotomy.

8. If a tracheotomy is done it is imperative to use as large a tube as possible in order to obtain an adequate airflow. The flow of air through a tracheotomy tube increases by the radius of the tube to the fourth power so that there is a tremendous increase in air flow when just one large size tube is used.

9. Atelectasis resulting from aspirated secretions or food is treated by immediate bronchoscopy and antibiotic therapy.

10. Abductor paralysis of the vocal cords can be treated only by immediate intubation or tracheotomy.

11. In 25 per cent of bulbar poliomyelitis patients, there is involvement of the respiratory center of the medulla resulting in inadequate ventilation, insufficient oxygen uptake, and a carbon dioxide retention. These cases should be treated with a mechanical respirator, tracheotomy, and supplementary oxygen therapy.

12. The vasomotor centers of the pons and medulla are implicated in some cases of poliomyelitis resulting in severe vasomotor disturbances. Treatment of this complication is unsatisfactory, but consists of oxygen therapy and supportive measures to combat shock.

13. Involvement of the pons may result in transient trismus which interferes with removal of secretions and feeding. This must be treated by tracheotomy and nasal feeding.

14. Pulmonary edema may result from an injury of the pulmonary capillaries by hypoxia or infection or from an increase of intracapillary pressure due to heart failure. This complication can be treated by transfusions of blood plasma, cardiac stimulants, and an avoidance of too rapid administration of intravenous fluids.

15. The acid-base balance is frequently disturbed and must be checked daily so that corrections can be made for any disturbances noted.

16. Involvement of the hypothalamus may result in hyperpyrexia, gastric hemorrhage, or gastric distention.

17. Hyperpyrexia may be avoided by placing these patients in an air-conditioned room, avoidance of hot packs, and proper cooling of the interior of the respirator. Once hyperpyrexia develops it is combated by antipyretics, alcohol sponges, massage of the limbs, and colonic irrigations with ice water.

18. Gastric hemorrhage may be a grave complication of poliomyelitis resulting in the sudden onset of shock in severe cases and gastric distress, "coffee ground" emesis, and confusion in milder

cases. Treatment follows that for gastric ulcer, with immediate transfusion, ulcer diet, and antacids.

19. Gastric distention occurs during convalescence and produces nausea, abdominal distention, and occasionally respiratory embarrassment and death.

20. Cerebral symptomatology may result from actual involvement of the brain by the virus or more commonly due to the associated hypoxia. In the latter case, the symptoms improve just as soon as the cause of the hypoxia is determined and remedied.

21. Drug therapy should be greatly restricted. Sedatives in particular, because of their depressant action, are contraindicated in all cases of poliomyelitis with involvement of the bulbar centers.

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The treatment of epilepsy is a subject on which numerical analysis gives little help. A large number of cases are under observation too short a time to enable the effect of remedies to be fairly estimated, and of the cases in which benefit is derived, we have no means of ascertaining how many relapse when treatment is discontinued. Of the cases analyzed, the effect of treatment was noted in 562. Complete arrest, for a time, was effected in 241; in most of these the fits remained absent as long as the patients were under observation, and some were heard of after the treatment was discontinued, and were still free from fits. In 266 cases improvement short of arrest was obtained, the fits being reduced, in many, to one-thirtieth, one-fiftieth, and even one-hundredth of their former frequency. In fifty-five cases no improvement was effected by any method of treatment.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

NEWSLETTER

MAY, 1954

AMERICAN ACADEMY OF NEUROLOGY

Howard D. Fabing, President
Walter O. Klingman, President-Elect
Francis M. Forster, Vice-President
Alexander T. Ross, Secretary
Dave B. Ruskin, Treasurer

Annual Meeting in Washington Biggest Ever

In the floral setting of Washington's spring, the 1954 annual meeting of the Academy held at the Shoreham Hotel outdistanced all previous meetings from the standpoints of attendance, organization, enthusiasm, and scientific reporting. Everywhere the gracious smile of President Howard D. Fabing continuously testifed to the success of the occasion. All activities proceeded on schedule, thanks to Frederick L. Stone, chairman of local arrangements.... The scientific sessions were both practical and revealing. Two deviations from past programs were a treatment symposium in neurologic conditions which neurologists are best qualified to treat, and short reports of unusual clinical entities. Other papers covered nearly all the new research activities in clinical and basic neurology.... According to Francis M. Forster, program chairman and Dean of the Georgetown University Medical School, "The Academy has become a focal point for the dissemination of scientific knowledge of neurology in the United States".... In 1955 the Academy meeting will be in Houston and in 1956 in St. Louis.

Special Courses Reach New Peak

The ever popular special review courses reached a new high in interest and enrollment at the Washington meeting. A total of 208 applications for these courses were accepted; many courses were way oversubscribed. Particularly popular was the course in neurophysiology, under James L. O'Leary of Washington University, which, besides the lectures, demonstrated living biologic preparations, some of which were presented at the National Institute of Neurological Diseases and Blindness.... This program will be continued in 1955 at the Houston meeting and a preliminary schedule already has been outlined by A. B. Baker, chairman of the committee on special courses. Included will be review courses in neuropathology, under Fae Tichy; collagen diseases, under Joe R. Brown; EEG, under Richard Zarling; and a course in the basic and clinical aspects of neuromuscular diseases from the National Institute of Neurological Diseases and Blindness.... Also, there will be a new course, designed for the general practitioners of Texas, on the diagnosis and treatment of common neurologic conditions encountered in general practice. The content of this course will be worked out by Benjamin Boshes in collaboration with local physicians in the Houston area.

Scientific Exhibits Draw Large Crowds The twenty scientific and six technical exhibits provided a neurologic education in themselves. Particularly highlighted was an exhibit of phase measurements in EEG by A. M. Andrew of M.I.T., a study of the "biochemical lesion" in epilepsy by Donald B. Tower; the case for nerve regeneration by William F. Windle; and diagnostic studies on deep cerebral veins by Barnard Wolf.... An innovation proving the growing liaison between neurologists and their patients was provided by exhibits from voluntary health agencies, including the National Society for Crippled Children and Adults, United Cerebral Palsy Association, the National Multiple Sclerosis Society, and the National Foundation for Infantile Paralysis.... According to exhibit chairman Benjamin Boshes, "The exhibits this year delineated clearly the large spectrum of neurologic disorders and demonstrated the need to bridge the gap between neurologic science and the public."

Academy Banquet Gala Occasion The annual Academy cocktail party and banquet, held in the Terrace Room of the Shoreham, set the stage for an interlude of camaraderie and merriment. More than 260 members and guests participated. Among the honor guests and their wives were: the Surgeon General of the Public Health Service, Dr. Leonard A. Scheele; Dr. W. H. Sebrell, Jr., director, National Institutes of Health; Brig.-Gen. R. E. Chambers, chief of professional division, Army Medical Department; Brig.-Gen. O. O. Benson, Jr., chief of medical staffing and education, Department of the Air Force; Captain Elmer S. Caveny, chief of psychiatry and neurology, Office of the Surgeon General of the Navy; and Dr. Harvey J. Tompkins, director, Psychiatry and Neurology Service, Veterans Administration. There were no speeches; the banquet was followed by dancing.... Distinguished guests present at the scientific sessions, but unable to attend the banquet, were Dr. Glidden Brooks of United Cerebral Palsy; Dr. C. H. Traeger, consultant to the National Multiple Sclerosis Society; Miss Jayne Shover, associate director of the National Society for Crippled Children and Adults; the Governor of Guam; as well as the noted science writers, Albert Deutsch, William Lawrence, and Nate Haseltine.

Judd Speaks on Southeast Asia Dr. Walter H. Judd, former physician at the Mayo Clinic and for many years a medical missionary in China, and now Republican representative from Minnesota, was the special speaker at the joint luncheon of the Academy and the Woman's Auxiliary. An authority on Far Eastern affairs, Congressman Judd spoke on the problem of China and the surrounding countries in relation to Russia's efforts for world conquest. While the loss of China and possibly the loss of Indo-

China to the Communists has put us on the defensive, Congressman Judd said, the control of the Far East is not totally lost. Fourteen countries border on China with a total population equal to China's, and these areas must receive our close support and aid if they too will not fall to Communist domination. He stressed the importance of a constructive program in Japan and of our support of the people of Southeast Asia, to prove to them that we are people of principle, that we stand behind them, and especially that we do not attempt to compromise with tyrants to achieve temporary security....Congressman Judd's address was listened to with intense interest by a capacity crowd which overflowed the large Blue Room of the Shoreham.

Letter to Auxiliary From Mrs. Eisenhower Delivered by a special courier from the White House was a letter from the First Lady expressing her appreciation for an objet d' art sent previously by the Auxiliary as a token of their esteem for Mrs. Eisenhower as a person and for her interest in the health problems of the nation. Mrs. Eisenhower's letter read: "Dear Friends: I do want each of you to know how completely delighted I am with the beautiful piece of Lalique glass which you left for me at the White House.... This is an exquisite gift, and one which I shall consider as a treasured possession. I especially like the flared sides of the dish and the lovely rose pattern in relief. ... I do wish it might have been possible for me to see you and thank each one personally for such kindness. I hope your visit in Washington has been a most pleasant one.... With my warmest good wishes to all of you, Mamie Doud Eisenhower."

Joint Session With Epilepsy League The Academy scientific program terminated in a joint session with the American League Against Epilepsy on May 1st. Featured in this program was a report of the legislative committee of the American League Against Epilepsy, by Roscoe Barrow, Dean of the College of Law, University of Cincinnati, and President Howard D. Fabing. Among the interesting facts revealed by the study were that 47 states prohibit driver's licenses for epileptics; 19 states prohibit issuance of marriage licenses to epileptics and in 4 of them it constitutes a crime; one state has sterilization laws, but no distinction is drawn between genetic and acquired epilepsy, and no state gives a definition of epilepsy.... On the basis of this report, a resolution was passed that the Academy and the American League Against Epilepsy prepare a recommendation for a revision of certain Federal and State statutes governing epileptics.... An account of the Epilepsy League meeting will be forthcoming in the next issue of the Newsletter.

EEG Society To Meet In Atlantic City The eighth annual meeting of the American Electroencephalographic Society will be held at the Hotel Claridge, Atlantic City, N. J. (June 11 to 13), preceding the annual meeting of the American Neurological Association (June 14 to 16). The scientific program of the EEG Society, which will begin Friday afternoon, June 11, consists of a symposium on the relationship of "The Rhinencephalon" to clinical EEG and experimental neurophysiology, under the chairmanship of Robert Schwab, and a special session on the medico-legal aspects of clinical EEG, moderated by A. Earl Walker. The annual banquet is scheduled for Saturday, June 12. Secretary of the Society is Dr. W. T. Liberson, VA Hospital, Northampton, Mass.

Van Buskirk Goes To Maryland Charles Van Buskirk, assistant professor of neurology at the University of Minnesota, has been appointed full time professor of neurology at the School of Medicine, University of Maryland, Baltimore. At his new post he proposes to establish a graduate training program in neurology for a minimum of three years, and in addition, to provide training in neurology for residents in neurosurgery, internal medicine, and psychiatry.

Kolb New Director of Psychiatric Institute Lawrence C. Kolb, consultant at the Mayo Clinic and chairman of the AAN committee on epidemiology, has been appointed director of the New York State Psychiatric Institute and professor of psychiatry at Columbia University. Previously, Dr. Kolb had been instructor of neurology at Johns Hopkins Medical School and director of research projects at the National Institute of Mental Health. He probably will assume his new duties in New York this fall.... Dr. Kolb succeeds Dr. Nolan D. C. Lewis, who retired last September.

Percival Bailey

CLINICAL PATHOLOGIC CONFERENCE

Raymond D. Adams, M.D.
Section Editor

Presented by Ben W. Lichtenstein, M.D.

CASE PRESENTATION

Clinical history: A 48 year old white male, who worked as a supervisor in a refinery plant, was referred to the Illinois Neuropsychiatric Institute on January 12, 1954. His chief complaints were chronic fatigue, forgetfulness, nervousness, and headache of one year's duration. There was a history of epigastric pain for four years and roentgenographic studies three years previously revealed evidence of a possible duodenal ulcer. The headache was bilateral, frontal, and throbbing in character and occurred daily, starting in the early morning, for about one year. From August 3 to August 20, 1953, he was studied in a large medical clinic where roentgenograms of the stomach revealed a pyloroduodenal deformity, the nature of which could not be determined from the films. At that time, he complained of a tendency to drag his right foot and, because of this symptom and the suggestive neurologic complaints of headache and nervousness, he was studied in the neurology section of the clinic but no positive evidence of organic disease of the nervous system was found. He also gave a history of substernal tightness occurring with exertion; electrocardiograms revealed evidence of myocardial damage. Because of the absence of organic findings of brain disease and the presence of evidence of coronary insufficiency and peptic ulcer, the headaches were attributed to a state of tension and he was advised to keep to a slower pace. He stated that his headache had improved for a time following a trip to Hot Springs, Arkansas in November 1953. In the last six months he noted that his right leg dragged when he walked; in the last two to three months there was more evidence of a staggering gait and he actually fell several times. His memory was not as sharp as in the past, and he developed emotional instability and cried while watching television programs.

His past history was not medically significant. General physical examination showed the patient to be comfortable, with a blood pressure of 115/70, pulse 84, and respiration rate 20. The chest was emphysematous, there was moderate obesity, and the prostate was slightly enlarged.

Neurologic examination: Examination of the optic fundi revealed slight congestion of the blood vessels about the disk which was thought by some examiners to be indicative of early papilledema. The pupils reacted to light and convergence and both the visual acuity and fields were within normal limits. The remainder of the cranial nerves showed no abnormalities. There were no sensory disturbances. Examination of the motor system revealed generalized weakness in all extremities but no evidence of muscle atrophy or abnormal movements. The deep reflexes were moderately exaggerated, the superficial abdominal reflexes were present, and no pathologic reflexes could be elicited. There was some incoor-

From the department of neurology and neurological surgery (Neuropsychiatric Institute), University of Illinois College of Medicine, Chicago.

dination in the right upper extremity, but both the finger-to-nose and heel-to-knee tests were within normal limits. The initial impression was that of a chronic brain syndrome possibly due to premature arteriosclerosis.

Hospital course: The patient was seen by several staff members, and because of the lack of localizing signs and rather doubtful papilledema, it was decided that a lumbar puncture could be performed safely. This was done on January 13, 1954 at 9:00 a. m. and the opening pressure was 190 mm. cerebrospinal fluid. After 7 cc. of clear, colorless fluid were removed, the final pressure was 100 mm. The patient felt fairly well all day and was asymptomatic until 4:00 a. m. the next day when he was found on the floor next to his bed. He was stuporous; both pupils were fixed, the left being larger than the right. There was generalized flaccidity, although the deep reflexes could be obtained, and Babinski signs were elicited bilaterally. At this time, it was learned that the total protein on the sample of cerebrospinal fluid was 124 mg. per cent. Urinalysis and blood counts were within normal limits. The patient remained stuporous, and early the same morning he was taken to the operating room where a left subtemporal decompression was performed. The dura was under great tension and attempts to reach the ventricular system were unsuccessful. The patient remained unresponsive and by 2:00 p. m. his temperature rose to 102.6° F. A roentgenogram of the chest revealed cloudiness of the pulmonary parenchyma suggestive of early pneumonia. The patient was given penicillin and antipyretics but remained in a critical state. About 4:50 p. m. he suddenly became cyanotic, respirations were very irregular, and the blood pressure reading could not be obtained. Within a few minutes the heartbeat stopped and he was pronounced dead at 4:57 p. m., slightly less than 32 hours after the lumbar puncture.

Clinical diagnosis: It was thought that death resulted from hemorrhage in a nonlocalized tumor of the brain.

CLINICAL DISCUSSION

DR. PERCIVAL BAILEY: The first question to be answered is, "Would you manage a similar case in the same manner in view of the fatal outcome?"

DR. JOSEPH LUHAN: It is reported that a 22 gauge needle was used. Do you believe that the cerebrospinal fluid pressure is accurate with such a needle?

DR. OSCAR SUGAR: Yes. The patient was fully relaxed and I think that the reading of 190 mm. was quite accurate.

DR. ADRIEN VERBRUGGHEN: I believe a crucial problem in this case is whether or not the patient did have papilledema. The presence of papilledema would lead me to do ventricular puncture rather than lumbar puncture.

DR. PAUL BUCY: The dilated, fixed pupil is strongly suggestive of a herniation of the hippocampus through the incisura.

DR. BAILEY: The fact that the patient was found in coma after being found on the floor is suggestive of a possible chronic subdural hematoma in view of the long history of headaches without positive neurologic signs and the sudden crisis with dilatation of the left pupil.

DR. VERBRUGGHEN: Yes, one would have to seriously consider a chronic subdural hematoma. Did roentgenograms of the skull help any?

DR. J. G. BYLA (resident physcian): Roentgenograms of the skull showed no abnormalities.

DR. FREDERIC GIBBS: An electroencephalogram may have helped in this case for, if there was a tumor in the cerebral cortex, one may have noted a slow wave focus.

DR. BUCY: What if it was a subdural hematoma?

DR. GIBBS: In some cases, there is an area of decreased voltage or a slow wave focus but sometimes the electroencephalogram is not diagnostic.

DR. BUCY: The history states that this man dragged his right leg. Were you able to notice any disturbance in gait?

DR. BYLA: No. When we examined him, there was no real disturbance in gait.

DR. LUHAN: Were there any mental symptoms other than the emotional instability and failing memory?

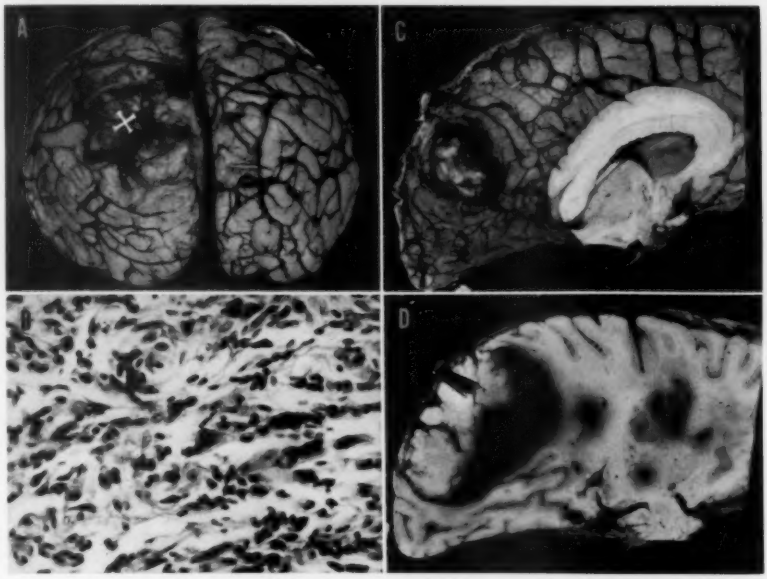

FIG. 1. A. Photograph showing the meningioma (X) in the left superior parietal-occipital region. *B*. Photomicrograph showing the histologic picture of the tumor. *C*. A view from the medial surface of the left hemisphere. *D*. A parasagittal section.

DR. BYLA: The family mentioned that he had periods of mental confusion.

DR. BAILEY: What was the purpose of the lumbar puncture in this case? Was it to obtain fluid for a Wassermann test or was it to measure the status of the cerebrospinal fluid pressure?

DR. BYLA: The papilledema was only questionable, and the lumbar puncture was performed to measure the pressure and to perform laboratory tests on the cerebrospinal fluid.

DR. BUCY: If the history is reliable, this man had progressive disease in the left cerebral hemisphere. A tumor is the most likely condition.

DR. ROLAND MACKAY: When in the course of this man's illness did definite signs of organic disease of the nervous system appear? You will recall that he was recently studied at a neighboring clinic and a diagnosis of tension headache was made because, despite his symptoms, there was no unequivocal evidence of organic disease of the brain.

DR. BUCY: The acute brain symptoms developed after the lumbar puncture.

DR. MACKAY: If this patient's condition had not deteriorated, would we consider a cerebrospinal fluid pressure of 190 mm. very significant?

DR. BUCY: What about the elevated cerebrospinal fluid protein?

DR. VERBRUGGHEN: Subdural hematoma is a likely diagnosis since the symptoms apparently came and went until his condition became critical with a dilated and fixed left pupil.

DR. LUHAN: The case sounds more like a neoplasm than a subdural hematoma.

PATHOLOGIC DISCUSSION

DR. LICHTENSTEIN: Examination of the brain revealed a meningioma in the superior medial aspect of the left posterior parietal region (figure 1). A parasagittal section of the left hemisphere 2½ cm. from the midline showed the meningioma invading and compressing the brain tissue. Its greatest anteroposterior diameter was 7 cm. and it extended into the brain for a distance of 4 cm. Examination of the inferior surface of the brain revealed herniation of cerebral tissue through the incisura, the herniation being most marked on the left side (figure 2). In addition to the hippocampal herniation, there was a herniation of the gyrus rectus over the limbus of the sphenoid bone. Such herniations are not rare but they are often overlooked. Removal of the hindbrain by a sharp incision through the midbrain revealed compression and distortion of the latter. The right half of the midbrain, especially the cerebral peduncle, was more compressed than the left half. Throughout the tegmentum and the peduncle there were focal and confluent pinpoint to pin-sized hemorrhages most marked on the right side (figure 2). The cisterna ambiens was almost completely obliterated and the interpeduncular cistern was greatly narrowed. In view of these facts, it is evident that this patient had had a neoplasm in the superior posterior portion of the left cerebral hemisphere for some time. The question may well be asked, "Did the lumbar puncture result in the herniations described or were they present for some time prior to the puncture?" It is well known that hernations of a similar nature may be present without benefit of lumbar puncture. Another question that may be asked is, "Can such herniations develop without extreme degrees of increased intracranial pressure?" The brain is a soft, semisolid substance which can be distorted without extreme degrees of increased intracranial pressure. I believe that the slowly growing meningioma compressed the brain tissue around it and forced portions of the pallium through the incisura without ever creating any greatly increased intracranial pressure. The gradual narrowing of the ambient cistern, however, resulted in actual encroachment upon the midbrain with compression of the vascular supply to this important structure. In such instances in which the ambient cistern is compressed, the margin of safety for lumbar puncture is greatly reduced and the removal of even small quantities of fluid may result in compression of the veins and petechial hemorrhages in the midbrain. The pupillary changes, stupor, and hyperpyrexia can all be attributed to the circulatory changes in the midbrain and neighboring hypothalamus. It is in these instances of slow compression of the contralateral cerebral peduncle by the free margin of the dura lining the incisura that hemiparesis on the homo-

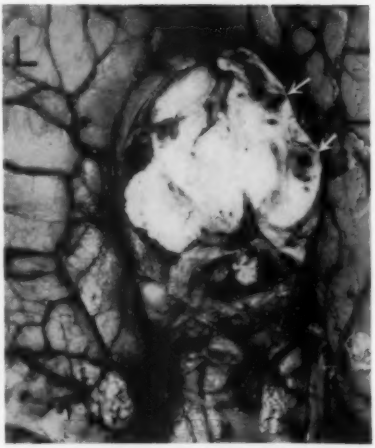

FIG. 2. Photograph of the base of the brain after removal of the hindbrain. Note the major herniations of cerebral tissue on the same side (L) as the meningioma, the compression of the right side of the midbrain (arrow), and the multiple hemorrhages.

lateral side frequently results. In this case, there was considerable question as to which lower extremity was actually weak but, when the patient passed into coma, Babinski signs were present bilaterally.

DR. BAILEY: If you suspect increased intracranial pressure, should one puncture the ventricle rather than the lumbar subarachnoid space?

DR. MACKAY: One would be doing many ventricular punctures with few positive results if one was fearful to perform lumbar puncture in a "suspected" case of increased intracranial pressure wtihout papilledema.

DR. BAILEY: Should ventriculography have been done?

DR. BUCY: You would get a lot of negative ventriculograms if you followed such a program.

DR. MACKAY: If the lumbar puncture produced the hernia, why the 15 hour interval?

DR. VERBRUGGHEN: Seepage from the lumbar puncture hole in the dura mater may be a factor.

DR. BAILEY: Should we have done an arteriogram in this case?

DR. SUGAR: From the location of the tumor, there is good likelihood that the arteriogram would have been negative. In such an instance of critical compression of the midbrain, should the tentorium be incised?

DR. BUCY: In such instances, the patient already has hemorrhages in crucial areas and I doubt that an incision would help.

DR. RALPH GERARD: What is the mechanism of the herniation?

DR. LICHTENSTEIN: I feel that the herniation in instances such as this results from migration of the semisolid brain tissue and it does not take much force to produce migration in the vicinity of the incisura. I realize that, in similar instances in which there is no papilledema and in which the recorded cerebrospinal fluid pressure is not elevated beyond its normal range, the statement is made that the patient must have had episodes of increased intracranial pressure to account for the herniations, but this may not be the case.

PATHOLOGIC DIAGNOSIS

Meningotheliomatous meningioma of the cerebral dura mater compressing and invading the left cerebral hemisphere in the superior parietooccipital region.

Herniation of cerebral substance caudally through the tentorium.

Compression of the midbrain and its blood vessels with secondary hemorrhages.

The treatment of megrim by measures directed to the improvement of the general health, or the correction of faulty hygienic conditions, is by no means the least important aspect of the subject. As we have already said, it is not that all or perhaps a majority of cases can be successfully treated in this way, for many habitual sufferers from megrim enjoy in other respects, and during the intervals of their attacks, very good health; and others suffer all the same, though leading the most regular, tranquil, abstemious, and otherwise healthy lives; but, according to my experience, the greater number of patients who seek medical advice for their complaint are those with whom it has been first awakened, or greatly aggravated, by failing health from other causes, or some injurious habits of life.

Edward Liveing in *On Megrim, Sick-Headache, and Some Allied Disorders,* published in 1873.

CASE REPORT

Polycythemia Complicated by Brain Tumor

Irwin Perlmutter, M.D. and Richard E. Strain, M.D.

POLYCYTHEMIA VERA is a disease of unknown origin, characterized by an excessive production of all the marrow elements with resultant increases in red cell, leukocyte, and platelet counts.[1] There is an increase in the hematocrit, slowing of the velocity of blood flow, and an increase of blood viscosity.

Symptoms referable to any organ of the body may develop, since all organs become distended with an excessive quantity of blood. In the case of the brain, which is enclosed in the rigid, non-yielding skull, symptoms brought on by plethora are accentuated. Headache, dizziness, and tinnitus are frequent complaints.[2] Indeed, Loman and Dameshek[2] state that in polycythemia symptoms referable to the head occur more frequently than those relating to any other body system. They state that polycythemia may cause changes indistinguishable from those caused by intracranial pressure of other causes.

Complications of polycythemia include a tendency both to hemorrhage and to thrombosis. Lesions of these types involving vasculature in the heart, brain, and mesentery are not uncommon. Cranial nerve palsies and "strokes" are the not infrequent results of either the thrombotic or hemorrhagic propensity.[3,4] The statement has been made, "It seems worthwhile to emphasize the nervous symptoms presented by patients with polycythemia vera, not because the case reports and various studies of this condition fail to make mention of their frequent occurrence, but because a failure to keep them in mind very often has led to diagnostic mistakes and in some instances to cerebral operations, with the idea that the symptoms were the result of brain tumor."[5]

It has also been stated that "the association of polycythemia rubra vera with intracranial neoplasia is an event of the greatest rarity."[6]

It is the purpose of this communication to report two patients in whom signs and symptoms of intracranial difficulty were caused by brain tumor and not by coincidentally-existing polycythemia vera. In one patient signs and symptoms due to an intracranial mass lesion were relieved temporarily by venesection for polycythemia. This type of relief of neurologic symptoms was reported

From the departments of neuropatology and neurosurgery, Mount Sinai Hospital of Greater Miami, Miami Beach, and the department of neurology and psychiatry, University of Miami School of Medicine, Coral Gables, Florida.

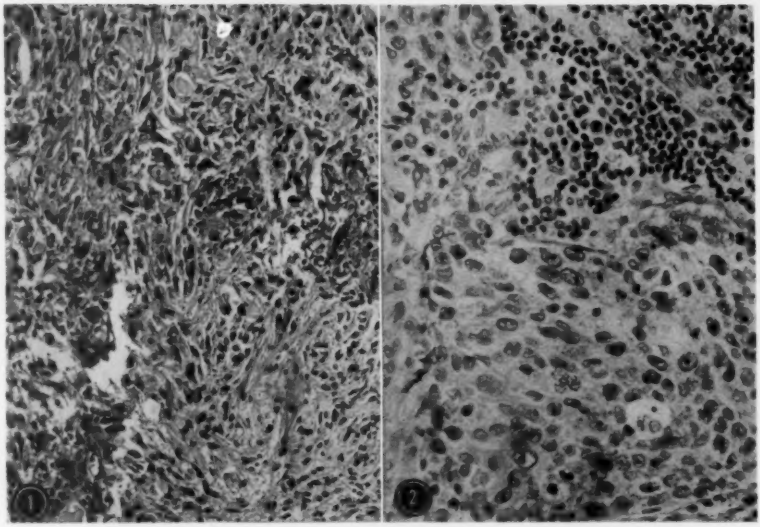

FIG. 1. Microphotograph of the tumor of case 1. Note pleomorphism of cell type, multinucleated giant cells, mitotic figures, endothelial budding, areas of necrosis.
FIG. 2. Microphotograph of the tumor of case 2. Note squamous epithelial cell type and mitotic figures.

by Loman and Dameshek[2] in a patient who had only polycythemia.

CASE REPORTS

Case 1.—A 52 year old woman was admitted to the hospital on July 5, 1952. About five years previously she had suffered a head injury, followed by convulsions and coma. A subdural hematoma was removed at another hospital and the patient made an uneventful recovery. Shortly thereafter she was found to be suffering from polycythemia vera, for which she was treated by venesection at intervals. During the six months prior to admission she had many emotional complaints related to family difficulties and was treated by a psychiatrist. At this time the neurologic examination was said to be entirely negative. There was no evidence of organic brain syndrome.

Three months before admission she was reexamined by the psychiatrist who found a definite memory defect and impairment of intellectual function. Because of these, an electroencephalographic record was made, which was reported to be normal. The family told of several episodes during which the patient became listless, refused food, seemed confused, and had difficulty in expressing herself. On at least one occasion she had donated blood at the blood bank, with temporary improvement in her state of responsiveness.

She had been hospitalized in June 1952 because of stupor. Within 48 hours she improved spontaneously and was discharged. During the next few weeks there was progressive deterioration. She ate little, and lost her ability to talk; her family felt that she understood although she could not communicate verbally. Two days before admission she became bedridden.

Physical examination: The patient was confused, and had a right hemiparesis and aphasia. There was no papilledema. Blood pressure was 120/70, pulse 72. Blood count: red blood cells 6,980,000; hemoglobin 105 per cent, or 16.4 gm.; white blood cells 13,900; platelets 1,400,000; hematocrit 63. Lumbar puncture showed an initial pressure of 250 mm. Xanthochromic fluid was obtained; the total protein was 116 mg. per cent. Roentgenogram of the skull showed

the pineal displaced 6 mm. to the right. The chest roentgenogram was negative.

Course: The patient was alternately alert and stuporous, and hemiparesis became more marked. On July 10, 1952, a ventriculogram was performed through the old burr holes. The subdural space did not contain a clot. Air filled only the right lateral ventricle, which was not displaced. On the basis of polycythemia it was felt that the patient had a vascular type of brain lesion.

For nine days following ventriculography the patient improved, and the neurologic consultant felt that rehabilitation should be started. However, her condition retrogressed and, with a terminal temperature rise, she expired on July 22, 1952.

Pathologic examination: There was a large grayish-brown and dark red, variegated colored tumor occupying the medial inferior portion of the left occipital and parietal lobes. Microscopically, there were areas of hemorrhage and necrosis, endothelial budding of capillaries, pleomorphism of cell type, mitoses, and multinucleated giant cells – the usual characteristics of glioblastoma multiforme.

Final clinical diagnosis: 1) Polycythemia vera; 2) cerebral thrombosis (venous?) due to polycythemia; 3) terminal bronchopneumonia.

Case 2.—A 56 year old man was admitted to the hospital on December 27, 1949, complaining of occipital headache of one year's duration which had been worse in the past three months. The history was obtained from friends who said that he had been polycythemic for the past four or five years, during which time there had been frequent epistaxes. He had suffered a mesenteric vein thrombosis, necessitating bowel resection at another hospital. However, he had always been able to take care of himself until six months prior to hospital admission, when he became confused, disoriented, slovenly, incontinent, and began to drag his left leg.

Physical examination: The patient was cyanotic, and was disoriented in all three spheres. His speech was thick and he was dull, drowsy, and dyspneic. The right optic disk was blurred and small fundal hemorrhages were present. The left optic fundus could not be seen because of a lens opacity. There was left hemiparesis with correspondingly hyperactive deep tendon reflexes. Blood pressure was 120/78. Blood count: red blood cells 5,400,000; hemoglobin 111 per cent, or 18 gm.; white blood cells 9,800. A chest roentgenogram showed several large, thin-walled, confluent cysts in the anterior inferior portion of the left upper lobe. Roentgenogram of the skull was negative. Lumbar puncture showed clear fluid at 52 mm. pressure; the total protein was 129 mg. per cent. A neurologic consultant diagnosed cerebral thrombosis due to polycythemia vera.

Course: The papilledema increased to 3 diopters, and stiff neck developed on January 20, 1950. A ventriculogram was performed which showed the left lateral ventricle to be displaced to the left in its anterior portion. Right frontal craniotomy with lobectomy was carried out and a large grayish tumor containing many small cystic areas was excised.

Pathologic examination: Microscopically, this tumor was composed of freely mitotic squamous epithelial cells.

Diagnosis: Metastatic brain tumor, probably bronchogenic.

COMMENT

Polycythemia vera is commonly complicated by organic neurologic difficulties produced by 1) plethora and 2) thrombosis and hemorrhage. It is a disease of middle and later life and may be accompanied by any of the diseases of these periods.[7] Since brain tumor, primary or metastatic, occurs so frequently in patients in these age groups, neurologic complaints in patients with polycythemia should be thoroughly investigated before they are diagnosed as due to vascular complications of the original disease. On the other hand the syndrome that occasionally accompanies hemangioblastomas of the cerebellum must be borne in mind. These tumors cause headache, dizziness, and tinnitus,[8,9] all of which may be symptoms of polycythemia vera. It is interesting to note that these neoplasms are sometimes associated with a "neurogenic" polycythemia.[6,10]

Because of the length of time that the blood dyscrasia was present before ap-

pearance of the malignant neoplasm, the relationship between polycythemia and the tumor in the cases reported here is certainly coincidental.

SUMMARY

Neurologic syndromes due to brain tumor occurred in two patients with known polycythemia vera.

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It is certain that convulsions may arise from these lower centres, since there exists in the medulla the "convulsive centre," by the agency of which they may still be produced in animals after the removal of the cerebral hemispheres. Moreover, in man, convulsions are caused, in rare cases, by diseases of the pons and medulla. These facts make it probable that, as Luciani has suggested, the medulla may play a secondary part in the production of the convulsions in epilepsy. But the clinical facts to suggest that the discharge ever commences in this situation in idiopathic epilepsy are, it must be confessed, scanty. Does the study of modes of onset help us in this particular? There is one group of aurae which may be regarded as supporting the view that the fits which they initiate take origin in the medulla. I refer to those which I have grouped as the pneumogastric aurae, consisting of epigastric sensations rising to the throat, choking, dyspnoea, palpitation. We know that the pneumogastric nucleus and respiratory centre are in close proximity to, and connection with, the convulsive centre, and it is readily conceivable that a commencing discharge in this situation may lead to disturbance of the respiratory and pneumogastric centres before it causes general convulsions. But on this point other facts must be taken into consideration. The phenomena of conscious sensation make it certain that the whole body is represented in the cerebral hemispheres. It is conceivable that when a discharge originates in certain parts of the hemispheres, the central structures connected with the vagus, or representing the respiratory processes, may be the seat of the first discharge, or may, at least, be the most sensitive to the commencing disturbance, and be the channel through which the consciousness is first impressed.

W. R. Gowers in *Epilepsy and Other Chronic Convulsive Diseases*, published in 1885.

Neurology BOOK REVIEWS

The Parietal Lobes.

Macdonald Critchley, M.D., F.R.C.P. 1953. Baltimore: The Williams and Wilkins Company; London: Edward Arnold and Company. 480 pages. 150 illustrations. $13.50.

For the past several years Dr. Macdonald Critchley has devoted a large part of his time and interest to a study of the symptomatology of lesions of the parietal lobes. He has now summed up these investigations in an outstanding monograph, in which he correlates his own extensive experience with the international literature on the subject.

The first two chapters deal with the anatomy of the parietal lobe and experimental physiologic observations. The detailed anatomy of the parietal lobe in man is preceded by a discussion of the comparative anatomy. Morphologic considerations include discussions of the cortex, white matter, myelinization, cytoarchitectonics, and vascular supply.

The remainder of the book is concerned with the clinical aspects of disease of the parietal lobes, and includes chapters on the following: general symptomatology; disorders of tactile function; disorders of motility; constructional apraxia; Gerstmann's syndrome; disorders of body-image; visual defects; disorders of spatial thought; disorders of language and of symbolic thought; general psychiatric considerations and the relation of parietal symptoms to dementia and hysteria; and dominance, including localization within the parietal lobe. In a concluding chapter he recapitulates and correlates his observations. The author not only describes in detail the variations in clinical symptomatology that may be associated with parietal lesions, augmented by case reports, but he also illustrates many tests designed to bring to light various facets of disturbed physiology of this portion of the brain.

One cannot but be impressed with the author's erudition – regarding the parietal lobe, neurology in all of its aspects, psychology and psychiatry, and general as well as scientific literature. Yet he modestly states, "there is something essentially artificial about a full-dress discussion limited to a sector of the cerebral hemisphere," and "It has repeatedly been emphasized that the parietal lobe is neither an anatomical nor a physiological unit, but merely that part of the convex surface of the cerebral hemispheres which happens to be covered by the parietal bone. A neurological study confined to the topic of parietal disease is likely to be rewarding only to a limited extent." These statements the reviewer would take issue with, for Dr. Critchley has not only stressed but also brought to our attention the multiple and varying functions of this portion of the brain – in sensation, motor control, gnosis, and language and thought production. In his lucid presentation and faultless diction he has done much to simplify a complex subject. This book will without a doubt become the classical reference work on the parietal lobe.

R. N. DE J.

Diagnosis and Localization of Brain Tumors: A Clinical and Experimental Study Employing Fluorescent and Radioactive Tracer Methods.

George E. Moore, M.D. 1953. Springfield, Illinois: Charles C. Thomas, Publisher. 217 pages. $10.50.

This is the story of the development of isotope tracer technics for the localization of brain tumors, written by a pioneer in the field. In a serious vein and yet in terms the physician can understand, the author recounts his experiences in the development of these diagnostic methods.

In considerable detail and with illustrative case reports, Dr. Moore reviews the technic of fluorescein localization of brain tumors. Briefly, his experiences with the ineffectual attempts to demonstrate neoplasms with colored dyes and radiopaque materials are discussed. The author then describes the use of radioactive materials to localize brain tumors preoperatively and at operation. Experimental brain tumors are discussed and a brief outline of some of the studies on the blood-brain barrier using radioactive substances is given. Reference is made to the work of others in the field so that a complete picture of the present state of radioactive diagnostic technics for the localization of brain tumors is presented. An appendix on some technical aspects of the equipment will be of value to anyone entering the field.

Although the text is not easy reading, the physician seeking a general survey of current views in this field will be well repaid for his efforts. Nowhere else can the data included in this book be found in such compact form. The significance and value of this book may be indicated by the fact that it received the Samuel D. Gross Award for 1950 from the Philadelphia Academy of Surgery.

A. E. W.

Nervous Transmission.

Ichiji Tasaki, M.D. 1953. Springfield, Illinois: Charles C Thomas, Publisher. 164 pages. 77 illustrations. $7.50.

This excellent book is a scientific autobiography of Dr. Tasaki's own work during the past 20 years. Since he has made many fundamental advances in our knowledge of peripheral nerves during that period, a collection and summary of his work is timely and important. Western biologists in the field of neurophysiology have become accustomed to teams of specialists using complex equipment to make even mundane contributions. Dr. Tasaki's results come mainly from the use of a clear eye and a steady hand, with an absolute minimum of equipment. The resulting simplicity adds elegance and power to his thesis. Dr. Tasaki was able to carry out this work almost isolated from the international community of scientists until the defeat of Japan again allowed him free access to his foreign colleagues.

The title of the book misleads and might be extended more accurately to be nervous transmission in peripheral myelinated axons. There is a short discussion of the relation of the main subject of the book to unmyelinated fibers and a very short discussion on some possible implications in the central nervous system and in peripheral endings. Dr. Tasaki's great contribution has been to show the special physiologic properties of the nodes of Ranvier and their great difference in behavior and properties to the internodal parts of the fiber. He does not go into the processes in-

volved in the production of the nerve impulse as an electrochemical phenomenon. The main point in his conclusions is that the process which occurs in the myelin covered part of the fiber between the nodes is a passive one, while the active physicochemical processes which make the transmission possible are localized at the nodes.

He has reached this conclusion mainly by work on isolated single fiber preparations. A particularly valuable part of the book is an appendix describing the methods of making such dissections. Using single nerve fibers, he proceeds to demonstrate the various classical properties of excitability and the electrical properties of nerve tissue and to show the marked inhomogeneity of these properties which occur between the nodes and the internodal regions. By measuring the current flow during impulse transmission, the electrotonic properties of the nerve, and impedance changes, he deduces the electrical constants of the nodes and internodes and compares them with those found in unmyelinated fibers. Next Tasaki considers the effect of these findings on the mechanism of the refractory period if propagation is no longer a spatially continuous process but intermittent from node to node. He then proceeds to show the effects of urethane and cocaine in blocking impulse transmission across the node with depression of the action potential and an unchanged resting potential. Finally he relates the electrical findings on single fibers to the type of record obtained from nerve trunks.

Dr. Tasaki has thus skillfully presented his case for the nodal monopolisation of activity and the book is most highly recommended to anyone interested in this basic aspect of peripheral nerve impulse transmission. P. D. W.

Parkinson's Disease and Its Surgical Treatment.

Leslie C. Oliver, F.R.C.S. 1953. London: H. K. Lewis and Company, Ltd.; New York: John de Graff, Inc. 87 pages. 12 figures. $2.50.

This short monograph begins with a brief review of the pathology and etiology of Parkinson's disease, followed by a resumé of the clinical picture and medical treatment. The text is brief and presented in a clear, concise fashion which the student or general physician will appreciate, but it adds little of interest for the experienced neurologist.

The author's discussion is based on the results of examinations of over a thousand patients with Parkinson's syndrome, of which 300 were hospitalized for detailed studies; of these, 93 were selected for surgical procedures. He presents an analysis of his results in performing 76 Putnam pyramidotomies on 70 patients. Individual case histories are reviewed. Similar analysis is made of 14 patients on whom the author divided the entire lateral column. The monograph concludes with a brief review of cortical and subcortical surgical procedures for the relief of parkinsonism, emphasizing cortical undercutting which was performed by the author on ten patients. Results are classified as successful, no change, worse, and deaths. They indicate that there is no truly satisfactory surgical treatment for parkinsonism at the present time.

The neurosurgeon will find this book of greater interest than the neurologist due to its surgical emphasis, but for a comprehensive review of parkinsonism it might be included in the neurologist's reading.

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In the other report, on 250 operations including abdominal and lower back as well as head, neck and chest surgery, Drs. C. F. Scurr and J. B. Wyman state that, "In every case a substantial fall in the arterial blood pressure was produced." These doctors occasionally used procaine amide (a relative of Novocain) to supplement the action of arfonad. They found that "By slowing or stopping the dosage of arfonad, the pressure was allowed to return towards normal levels during the operation and then lowered again to meet surgical needs." They add that "It was possible to obtain the required degree of hypotension in a much higher percentage of cases than with any other agent."

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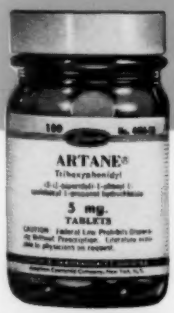

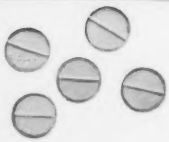

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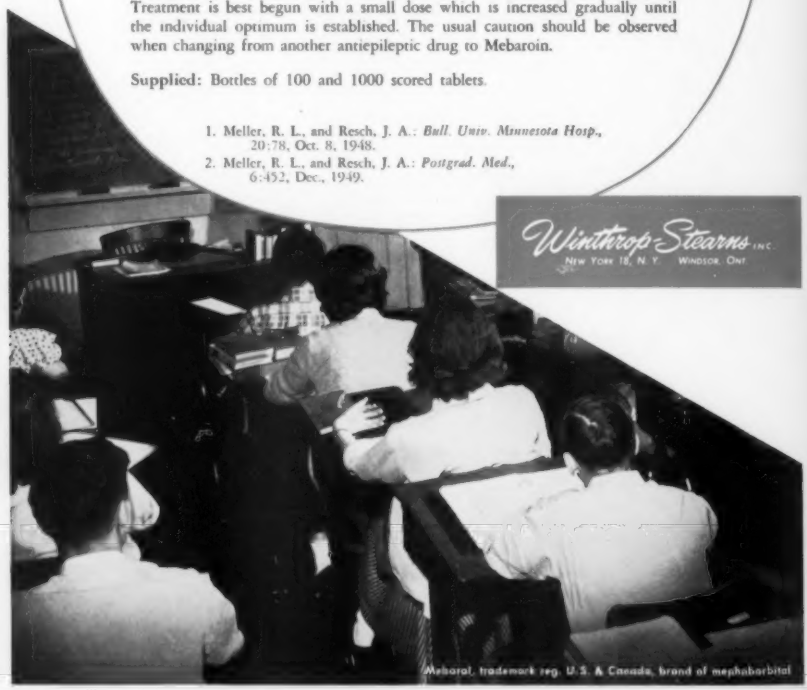

Mebaral, trademark reg. U.S. & Canada, brand of mephabarbital